THE BULLETIN OF Mathematical BIOPHYSICS

THE UNIVERSITY OF CHICAGO PRESS · CHICAGO · ILLINOIS

VOLUME 4-6
1942-1944

PUBLISHED MARCH, JUNE, SEPTEMBER AND DECEMBER, 1942
PRINTED BY THE DENTAN PRINTING CO., COLORADO SPRINGS, COLORADO

THE BULLETIN OF Mathematical BIOPHYSICS

THE UNIVERSITY OF CHICAGO PRESS · CHICAGO · ILLINOIS

VOLUME 4
NUMBER 1
MARCH 1942

THE BULLETIN OF Mathematical Biophysics

EDITED BY N. RASHEVSKY

The Bulletin is devoted to publications of research in Mathematical Biophysics, as described on the inside back cover.

THE BULLETIN is published by the University of Chicago at the University of Chicago Press, 5750 Ellis Avenue, Chicago, Illinois, quarterly, in March, June, September, December. ¶The subscription price is $2.50 per year, the price of single copies is 75 cents. Orders for service of less than a full year will be charged at the single-copy rate. ¶Patrons are requested to make all remittances payable to The University of Chicago Press in postal or express money orders or bank drafts.

THE FOLLOWING are authorized agents:

For the British Empire, except North America, India, and Australasia: The Cambridge University Press, Bentley House, 200 Euston Road, London, N.W. 1. Prices of yearly subscriptions and of single copies may be had on application.

For Japan: The Maruzen Company, Ltd., Tokyo.

For China: The Commercial Press, Ltd., 211 Honan Road, Shanghai.

CLAIMS FOR MISSING NUMBERS should be made within the month following the regular month of publication. The publishers expect to supply missing numbers free only when losses have been sustained in transit, and when the reserve stock will permit.

BUSINESS CORRESPONDENCE should be addressed to The University of Chicago Press, Chicago, Ill.

COMMUNICATIONS FOR THE EDITOR and manuscripts should be addressed to N. RASHEVSKY, Editorial Office of the Bulletin of Mathematical Biophysics, 5822 Drexel Avenue, Chicago, Ill.

PRINTED BY THE DENTAN PRINTING CO., COLORADO SPRINGS, COLORADO

Per.
QH
505
.A1
B874
v.4-6

BULLETIN OF

Mathematical Biophysics

CONTENTS

DIFFUSION AS A FUNCTION OF AGGREGATION IN COLLOIDAL MEDIA - - - - - - - - - 1
HERMAN BRANSON

A THEORY OF STEADY-STATE ACTIVITY IN NERVE-FIBER NETWORKS: IV. *N* CIRCUITS WITH A COMMON SYNAPSE - - - - - - - - - 7
ALSTON S. HOUSEHOLDER

A KINETIC THEORY OF DIFFUSION FORCES IN METABOLIZING SYSTEMS - - - - - - - - - 15
H. D. LANDAHL

SUGGESTIONS FOR A MATHEMATICAL BIOPHYSICS OF AUDITORY PERCEPTION WITH SPECIAL REFERENCE TO THE THEORY OF AESTHETIC RATINGS OF COMBINATIONS OF MUSICAL TONES - 27
N. RASHEVSKY

NON-LINEAR EXCITATION THEORY: NON-ACCOMMODATIVE, SUB-THRESHOLD EFFECTS - - - 33
ALVIN M. WEINBERG

VOLUME FOUR MARCH 1942 NUMBER ONE

IMPORTANT ANNOUNCEMENT

The increase in the output of papers in the field of mathematical biophysics makes it difficult to insure prompt publication without an increase in the size of the journal. Therefore, the Bulletin of Mathematical Biophysics inaugurates the following service:

Upon acceptance of a paper, the Editor, if necessary, will ask the author to shorten the paper to an extent dictated by the requirements of a reasonably prompt publication. The shortening should in no case reduce the paper to a mere abstract. Such a shortened paper will be published within six months or less.

The unabbreviated original manuscript will be kept on file at the editorial office. Any person desiring to avail himself of the complete manuscript, may obtain promptly a microfilm copy of the latter, at the cost of 1¢ per page plus postage, by applying to the Editorial Office, 5822 Drexel Avenue, Chicago, Illinois.

All papers in the Bulletin which have been thus shortened, will be marked at the end by the symbol MF, followed by a figure, indicating the number of doublespaced typewritten pages of the unabbreviated manuscript.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

DIFFUSION AS A FUNCTION OF AGGREGATION IN COLLOIDAL MEDIA

HERMAN BRANSON
HOWARD UNIVERSITY, WASHINGTON, D. C.

With the assumption that adsorption is a simple function of surface area, an analytical treatment is given for the dependence of the diffusion coefficient of an adsorbable solute upon the degree of aggregation of the adsorbing colloid. A simple relation is deduced after introducing some approximations. Some implications of the final diffusion equation are given.

The effects which colloids may have upon diffusion have been discussed qualitatively by N. Rashevsky (1938) and the specific problem of the adsorption of a diffusing solute by a single type of colloid has been treated by J. M. Reiner (1939). This note reports an investigation of a general phenomenon in a colloidal medium: with the assumption that adsorption is a simple function of surface area what could we expect to be the effect upon the diffusion coefficient of an adsorbable solute of the continued aggregation of the adsorbing colloid. This discussion proceeds under some plausible assumptions which simplify the analysis. The results are finally related to certain membrane phenomena of the cell.

The system we consider has initially simple, colloid particles and solute particles. The primordial colloid particles coalesce giving larger particles of uniform surface, uniformly distributed. If the initial number of simple colloid particles is designated by N_c and the initial number of neutral solute by N_s, the relationships which must always be met are

$$\begin{aligned} N_s &= n_s + \sum_{l=1}^{r} \sum_{k=1}^{m} ln(l, a, k) \\ N_c &= \sum_{l=1}^{r} \sum_{k=1}^{m} k[n(c, k) + n(l, a, k)] \ , \end{aligned} \tag{1}$$

where $n(l, a, k)$ designates the number of k-th-aggregated colloid particles with l adsorbed solute particles, $n(c, k)$ is the k-th-aggregated colloid particles having no adsorbed solute particles, and n_s is the number of solute particles not adsorbed. The types of possible re-

actions taking place in the system may be written

$$\begin{aligned} &n(c, 1) + n_s \rightarrow n(1, a, 1) \\ &n(1, a, 1) + n(c, 1) \rightarrow n(1, a, 2) \\ &\cdots\cdots\cdots\cdots \\ &n(c, i) + n(c, j) \rightarrow n(c, i + j) \\ &n(i, a, r) + n_s \rightarrow n(i + 1, a, r) \end{aligned} \tag{2}$$

provided $i + 1 \leqq r^{2/3}$. This condition is explained below. The first three reactions express the general assumption that a solute particle may be adsorbed by a single colloid particle but that the aggregate cannot adsorb another solute particle until the surface is at least twice the surface of the single colloid particle. Any other reaction of agglomeration is possible in the system so long as it does not violate this principle.

Nevertheless two particles having such a number of adsorbed particles that the complex formed by their agglomeration would have more than the allowed number of adsorbed solute particles were they all retained, can still agglomerate with the release of solute particles. This is expressed by adding to (2)

$$\begin{aligned} &n(1, a, 1) + n(1, a, 1) \rightarrow n(1, a, 2) + n_s \\ &\cdots\cdots\cdots\cdots \\ &n(k, a, m) + n(j, a, r) \rightarrow n(q, a, m + r) + ln_s \end{aligned} \tag{3}$$

where $(m + r)^{2/3} - 1 < q \leqq (m + r)^{2/3}$, $k + j = q + l$.

For simplicity the reactions are assumed to be irreversible. With these assumptions the maximum number of adsorbed particles is easily deduced. If we let v_1 , r_1 , and s_1 represent the volume, radius and surface of a single colloid particle and v_k , r_k , and s_k the same for an aggregate of k particles, we have

$$v_k = \frac{4}{3}\pi r_k^3 \; ; \quad s_k = 4\pi r_k^2$$

$$v_k = kv_1$$

since the k aggregate to form a spherical cluster, $kr_1^3 = r_k^3$ thereupon $s_k = 4\pi k^{2/3} r_1^2 = k^{2/3} s_1$. The maximum number of adsorbed solute particles on an aggregate of k colloid particles is

$$l = k^{2/3} \qquad \text{if } k \text{ is an integer,}$$

$$k^{2/3} - 1 < l < k^{2/3} \qquad \text{if } k \text{ is not an integer,}$$

which we have already used in (2) and (3).

Some hint as to possible numerical values for the maximum number of colloidal particles which may aggregate before flocculation can be taken from the specification of the range of colloidal particle size, the diameters ranging from 10^{-7} to 10^{-5} cm. Assuming that our primoridal colloid particle has the smaller diameter and the largest the larger, we have the maximum for $m \sim 10^6$ and the maximum for $r \sim 10^4$.

The solute particles are taken as uncharged so Fick's law for the transport of solute is

$$J = J_s + \sum_{l=1}^{r} \sum_{k=1}^{m} J(l, a, k), \tag{4}$$

in which J is the number of solute particles passing through unit surface in unit time whether as simple solute or in aggregate. The l, k, r, and m are the same as in (1). The $J(l, a, k)$ may be written

$$J(l, a, k) = -D(l, a, k) \operatorname{grad} n(l, a, k). \tag{5}$$

Introducing (5) into (4) with the corresponding forms for J_s and $J(l, a, k)$ and with the dependence of n_s and $n(l, a, k)$ on the positional coordinates expressed through N_s, we have

$$-D \operatorname{grad} N_s = -D_s \operatorname{grad} n_s - \sum_{l=1}^{r} \sum_{k=1}^{m} D(l, a, k) \operatorname{grad} n(l, a, k)$$

or

$$D = D_s \frac{\partial n_s}{\partial N_s} + \sum_{l=1}^{r} \sum_{k=1}^{m} D(l, a, k) \frac{\partial n(l, a, k)}{\partial N_s}. \tag{6}$$

D is the effective diffusion coefficient of the solute. Using (1) this becomes

$$D = D_s \left[1 - \sum_{l=1}^{r} \sum_{k=1}^{m} l \frac{\partial n(l\ a\ k)}{\partial N_s} \right] + \sum_{l=1}^{r} \sum_{k=1}^{m} D(l, a, k) \frac{\partial n(l, a, k)}{\partial N_s}. \tag{7}$$

Inasmuch as the adsorbed solute particles do not appreciably affect the bulk of the colloid aggregates we may take $D(l, a, k) = D(c, k)$ for all values of k. Furthermore on the basis of Einstein's law of diffusion the diffusion coefficient of an aggregate of h colloid particles is related to that of an aggregate of one solute particle and one solute particle by

$$D(c, h) = \frac{D(c, 1)}{h^{2/3}}. \tag{8}$$

These substitutions simplify (6). There remains, however, the rather complex double summations. We can approximate them through

$$\sum_{l=1}^{r} \sum_{k=1}^{m} l\, n(l, a, k) \backsim \beta(p) n(r, a, p) \tag{9}$$

$$\sum_{l=1}^{r} \sum_{k=1}^{m} n(l, a, k) \backsim \alpha(p) n(r, a, p) . \tag{10}$$

Without reference to the coefficients or to the first and last symbols in the parentheses we see that the $n(l, a, k)$ are merely the number of particles of each size group in the system. The mechanism here described places all the particles initially in $n(1, a, 1)$, thus initially (10) could be replaced by $n(1, a, 1)$. As time goes on, other $n(l, a, k)$'s will arise but the most unlikely distribution, one perfectly flat, would lead to a multiplicative factor equal to the number of particle sizes. For any other distribution the factor for any p would be in general a function of p but less than p. The factor $\beta(p)$ would behave in the same manner, although the numerical value would be different from that of $\alpha(p)$. We can relieve ourselves from too much specificity by putting

$$\alpha(p) = p^a, a < 1; \beta(p) = p^b, \ b \leqq 1 .$$

On closer inspection, (10) is seen to be equivalent to replacing the size-distribution curve by a rectangle of height $n(r, a, p)$ and width $\alpha(p)$. In (9) we replace the three dimensional distribution by a solid of cross-sectional area $\beta(p)$ and height $n(r, a, p)$. It is of interest to observe that p will be a function of time, for the distribution curve of particle size will move towards the maximum size with increasing time. Instead of the variation of $n(r, a, p)$ with time we think it best to keep p, which we shall call the degree of aggregation, as the independent variable.

If $N_s > N_c$ then practically all the N_c will be used as $n(1, a, 1)$ before the formation of any higher associated particles. This permits the division of the problem into two sections, the initial aggregation to form $n(1, a, 1)$ and the subsequent reactions to form higher aggregates. This first is essentially J. M. Reiner's problem. Both are contained in our analysis as we see upon introducing the approximations and the relations

$$n(l, a, p) \backsim \frac{n(1, a, 1)}{p} = \frac{N_c}{p} \quad \text{and} \quad N_c = \varepsilon N_s, \ \varepsilon < 1,$$

whence

$$D = D_s \left[1 - p^a \frac{\partial n(l, a, p)}{\partial N_s} \right] + \frac{D(1, a, 1)}{p(2/3 - b)} \frac{\partial n(l, a, p)}{\partial N_s}$$
$$= D_s \left[1 - \frac{\varepsilon}{p(1 - a)} \right] + \frac{\varepsilon D(1, a, 1)}{p(5/3 - b)}. \tag{11}$$

In terms of time, (11) holds from t_1 to t_m where $(t_1 - t_o)$ would be the time required for all N_c to become $n(1, a, 1)$ and $t_m - t_1$ would be the time for the formation of maximum size. For $t_o \leqq t \leqq t_1$ Reiner's (3) holds

$$D = D_s \left[1 - \frac{\partial n(1, a, 1)}{\partial N_s} \right] + D(1, a, 1) \frac{\partial n(1, a, 1)}{\partial N_s},$$

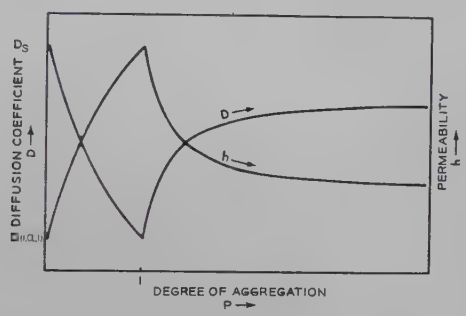

FIGURE 1

which is observed to be the same as our (11) with $p = 1$. Represented graphically these equations join exactly at $p = 1$ as is shown in Figure 1.

The removal of the assumption that $N_s > N_c$ and the precise sequential reactions do not influence the shape of the curve. This would not contradict (3) so long as the binding energy of colloid for colloid is not considerably greater than that of colloid for solute. It may cause a smoother transition at the minimum and a raising of the minimum so that D does not reach $D(1, a, 1)$. Furthermore we need not limit the number of adsorbed particles to one for the surface area of a simple colloid particle. If we would consider the number of adsorbed particles per cm², then the resulting curve for the variation of the diffusion coefficient would probably have the same shape. We may also weaken the requirement that the agglomeration gives spherical particles by introducing a shape factor γ, so that

$$s_k = \gamma\, k^{2/3}\, s_1, \qquad k^{1/3} > \gamma \geqq 1.$$

The shape factor will be a function of k, the number of particles in

the complex. With our assumptions the inclusion of this factor would raise the maximum for 1 with a given k to $\gamma\ k^{2/3} - 1 < l \leqq \gamma\ k^{2/3}$ but would cause no change in the other equations.

E. L. MacBain's data on the diffusion coefficient of long chain sulfonic acids, C_{10} to C_{14}, exhibit a minimum at dilute solution followed by a rise at higher concentrations. The curve is similar to Figure 1 but the data do not seem susceptible to interpretation by our mechanism These experiments are instructive, however, in calling our attention to the fact that the D-p curve in Figure 1 could be transferred into a D-concentration curve. Since the aggregation is directly proportional to the concentrations by measuring the diffusion coefficient of various concentrations of N_s and N_c a test of the mechanism outlined here could be carried through so long as the degree of aggregation does not vary appreciably during an experimental determination.

If the reaction takes place within a cell we may take $N_s = q_s t$ and $N_c = q_c t$ where the q's are the average rates of production of the solute and the adsorbing particle within the cell. In (11) ε would be q_c/q_s. For sufficiently rapid aggregation the action of this mechanism within a cell may give a purely physical interpretation of certain trigger mechanisms and other aspects of cellular behavior.

The rather simple extension that the presence of n_s primes the release of n_c in spurts gives a sinusoidal curve for the variation of the diffusion coefficient.

Finally the view that the diffusion solute lowers the permeability of the cell membrane to another diffusing substance admits a variation of the membrane permeability, h, inverse to that of D in Figure 1.

The author wishes to express his thanks to the Julius Rosenwald Fund for a grant which supported this investigation. He wishes also to acknowledge the helpful suggestions of Prof. N. Rashevsky out of which came this problem and the discussions with the University of Chicago group of mathematical biophysicists. The author is especially indebted to Dr. Alvin Weinberg who read the paper and made some valuable suggestions.

LITERATURE

MacBain, E. L. 1939. "Diffusion of Long-Chain Sulfonic Acids." *Proc. Royal Soc. A*, **170**, 415-423. See also the discussion of these data by G. S. Hartley. 1939. *Faraday Soc. Trans.*, **35**, 1109-1113.

Rashevsky, N. 1939. *Mathematical Biophysics.* Chicago: The University of Chicago Press.

Reiner, John M. 1939. "Diffusion in Colloidal Media." *Bull. Math. Biophysics*, **1**, 143-149.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

A THEORY OF STEADY-STATE ACTIVITY IN NERVE-FIBER NETWORKS: IV. *N* CIRCUITS WITH A COMMON SYNAPSE

ALSTON S. HOUSEHOLDER
THE UNIVERSITY OF CHICAGO

Conditions under which either of two distinct activity patterns may arise from the same stimulus pattern are deduced for the case of a network which consists of N simple circuits all joined at a common synapse. If the product of the activity parameters of all the fibers in any circuit is called the activity parameter of the circuit, or, more briefly, the circuit parameter, then the condition for the existence of such mutually consistent activity patterns is that there be a sum of circuit parameters which is not less than unity.

The general problem which is being discussed is twofold: first, to characterize those fiber networks, in which the activity pattern (AP) is uniquely determined by the stimulus pattern (SP); and second, for those networks which do not possess this unicity property, to characterize those pairs of AP's which are consistent with the same SP. In previous papers (Householder, 1941; these papers will be referred to here as I, II and III) this problem was solved for the simple-circuit case, and reference is to be made to them for these results and for the assumptions and terminology here employed. We remark only that the linear case alone (steady-state response a linear function of the constant stimulus) is being considered at present.

In working toward the case of the most general possible networks, we proceed now to the case of next greater generality beyond that of the simple circuit. We consider a network which consists of N circuits. The fibers in the J-th circuit are represented by

$$(1_J), (2_J), \cdots, (n_J). \tag{1}$$

Here and hereafter, *when not further restricted, the indices*

$$H, I, J, K, \cdots = 1, 2, \cdots, N; \tag{2}$$

and

$$i_J, j_J, \cdots = 1_J, \cdots, n_J. \tag{3}$$

The sub-index J will be omitted in cases where it is evident from the context, or where it is not necessary to make the specification. All fibers n_J terminate together and synapse with all fibers (1_K), thus connecting all the circuits at this synapse. Moreover in any circuit

J, the first fiber, the first two fibers, $\cdots$, or the first $n_J - 1$ fibers may be identical, fiber for fiber, with the corresponding first fiber or fibers

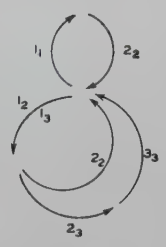

FIGURE 1

of some other circuit, but beyond these the two circuits have neither fibers nor synapses in common. The figure pictures such a set of three circuits in which the fibers (1_2) and (1_3) are identical.

In II we classified all fibers of a circuit into "even" and "odd". This classification can be made as follows: the *first fiber in the circuit is odd; the* i_J*-th fiber is odd provided the product of the activity parameters of the fibers which precede it in the circuit is positive; otherwise the fiber is even.* In the present case, the "first" fiber is determined by the structure of the system, and the classification is unambiguous. We shall call an *AP "even" ("odd') for a given circuit or set of circuits* provided all its zeroes in that circuit, or those circuits are at even (odd) fibers.

The quantities y_i, z_i, σ_i can be defined exactly as before, with the understanding that some of these quantities are identical when there are fibers common to two or more circuits, and that

$$S_{1_J} = S_{1_K} \tag{4}$$

for every J and K. Also it is, of course, tacitly understood throughout that the *possible AP's* are always limited by the fact that the same stimulus acts upon all the "first" fibers, so that when, for example, fiber (1_J) is active, every fiber (1_K) which has a lower threshold, is necessarily also active.

There is also a further limitation upon the possible *AP's* for the system. It was shown in III that for a simple circuit it is possible to have complete activity only when the product of the activity parameters of the circuit is less than one (algebraically. Thus complete activity is always possible in a circuit having an odd number of inhibitory fibers, for the product is negative, and hence less than one). An analogous argument can be used to show that

LEMMA 1. *In a multiple circuit of the type under discussion, complete activity in the steady state is possible if and only if the prod-*

uct of the activity parameters of any circuit and every sum of such products is less than unity.

The proof depends upon the fact that if

$$A_J = a_{1_J} a_{2_J} \cdots a_{n_J} , \tag{5}$$

and if

$$\Delta_J = 1 - A_J , \qquad \Delta_{JK} = 1 - A_J - A_K , \cdots ,$$

$$\Delta_{1, \dots , N} = 1 - \sum A_J \tag{6}$$

then $\Delta_{1, \dots , N}$ is the determinant of the equations in y_i which we obtain when we set every $\alpha_i = a_i$.

We therefore confine our attention to *AP*'s of the following type, which we shall call *admissible*:

a) if a fiber (1_J) is inactive, then every fiber (1_K) with the same or a higher threshold is also inactive;

b) if any component simple circuit is completely active, say the J-th, then $A_J < 1$, and every sum of such A_J's is less than one.

We now state the principal result, after which this will be proved by a sequence of lemmas.

THEOREM. *In the multiple circuits described above, let* α *and* β *be distinct admissible* AP*'s, and let* α_{0_J} *represent the set of zeroes of* α *in the* J*-th circuit,* β_{0_J} *the set of zeroes of* β *in the* J*-th circuit. Let the circuits be so enumerated that for* $J \leqq M$, α_{0_J} *and* β_{0_J} *have no members in common; for* $M < J \leqq M'$, α_{0_J} *and* β_{0_J} *are null sets; for* $M' < J \leqq N$, α_{0_J} *and* β_{0_J} *have at least one common member for each* J*. Then for the existence of a* σ *consistent with both* α *and* β *, it is necessary and sufficient that*

i) *every member of* α_0 *which is not also a member of* β_0 *is even, and every member of* β_0 *which is not also a member of* α_0 *is odd, or else the reverse is true;*

ii) *for every* $J > M'$, *if* j_J *is a member of both* α_0 *and* β_0 *, and if there is an* i_J *which is a member of one but not of both* α_0 *and* β_0 *, then* $i < j$;

iii) *for* $J \leqq M$ *, there is at least one* $A_J > 0$ *, and the sum of all the positive* A_J *added to* $A_{M+1} + \cdots + A_M$ *, is not less than one.*

Consider first the case that α and β have no common zero. For the sake of more compact expression we introduce the following notations:

for $h \varepsilon \alpha_0$ *read "h* is a zero of α";

for $h \varepsilon \alpha_0 + \beta_0$ *read "h* is either a zero of α or a zero of β".

Let

$$w_h = \begin{cases} y_h & \text{when} \quad h \,\varepsilon\, \beta_0 , \\ z_h & \text{when} \quad h \,\varepsilon\, \alpha_0 . \end{cases} \tag{7}$$

Let

$$[h, k] = [k, h] = \begin{cases} +1 & \text{when} \quad h, k \,\varepsilon\, \alpha_0 \quad \text{or} \quad h, k \,\varepsilon\, \beta_0 , \\ -1 & \text{when} \quad h \,\varepsilon\, \alpha_0 \quad \text{and} \quad k \,\varepsilon\, \beta_0 . \end{cases} \tag{8}$$

The w and the bracket symbols are not defined for other values of the indices. Let

$$A_h^{k+1} = a_h \, a_{h+1} \cdots a_k \quad \text{when} \quad 1 \leqq h < k \leqq n_J . \tag{9}$$

LEMMA 2. *If* $\mathrm{h}, \mathrm{k} \,\varepsilon\, \alpha_{0_J} + \beta_{0_J}$ *and* $1 \leqq \mathrm{h} < \mathrm{k} \leqq \mathrm{n}_J$; *then*

$$w_k \leqq [h, k] \, A_h^k \, w_h , \tag{10}$$

the symbols being defined by (7), (8) *and* (9). Except for the symbols, this is identical with lemma 3 in II, proved there for the simple circuit. The same proof applies here.

In each of the first M circuits there is a member of $\alpha_0 + \beta_0$. Let h_J represent the first of these, k_J the last, in the J-th circuit. The case $h_J = k_J$ is not excluded. To further simplify the notation, let

$$\begin{aligned} Y_K &= y_{n_K} , & Z_K &= z_{n_K} , \\ y_K &= y_{1_K} , & z_K &= z_{1_K} , \\ \eta_K &= y_{k_K} , & \zeta_K &= z_{k_K} , \\ \eta'_K &= y_{h_K} , & \zeta'_K &= z_{h_K} , \\ w_K &= w_{k_K} , & w'_K &= w_{h_K} . \end{aligned} \tag{11}$$

Furthermore, since the discussion is somewhat different for the first M and the last $N - M$ circuits, let the indices have the ranges

$$J, K = 1, 2, \cdots, M ; \qquad H, I = M + 1, \cdots, N , \tag{12}$$

while

$$L = 1, 2, \cdots, N . \tag{13}$$

Now each fiber (1_L) is acted upon by all the active fibers (n_L) as well as by the external stimulus S_1. Hence

$$\begin{aligned} y_L &= \sigma_{1_L} + \sum \alpha_{n_J} Y_J + \sum a_{n_H} Y_H , \\ z_L &= \sigma_{1_L} + \sum \beta_{n_J} Z_J + \sum a_{n_H} Z_H , \end{aligned} \tag{14}$$

so that

$$y_L - z_L = W \tag{15}$$

is independent of L. Also by lemma 1,

$$\eta'_J - \zeta'_J = A^{h_J}_{1_J}(y_J - z_J) = A^{h_J}_{1_J} W. \tag{16}$$

Since the sign of the left member of (16) depends only upon whether $h_J \varepsilon \alpha_0$ or $h_J \varepsilon \beta_0$, this equation together with lemma 2 establishes the necessity of condition (i) in the theorem.

Now by the lemma proved in III, if we subtract the second of equations (14) from the first we have

$$W = \sum A^{1_{K+1}}_{k_K} u_K + \sum A_H (y_H - z_H), \tag{17}$$

where

$$u_K = \begin{cases} \eta_K & \text{if } k_K \varepsilon \beta_0, \\ -\zeta_K & \text{if } k_K \varepsilon \alpha_0. \end{cases} \tag{18}$$

But by (15) and (16), (17) is equivalent to

$$\Delta_{M+1, \dots, N} W = \sum A^{1_{K+1}}_{k_K} u_K, \tag{19}$$

and by lemma 1 this $\Delta > 0$ since α and β are both admissible. Again by the lemma from III,

$$\eta'_J - \zeta'_J = A^{h_J}_{1_J}(y_J - z_J),$$

so that

$$\Delta_{M+1, \dots, N}(\eta'_J - \zeta'_J) = A^{h_J}_{1_J} \sum A^{1_{K+1}}_{k_K} u_K. \tag{20}$$

Since the Δ is positive, each member of (20) is positive when $h_J \varepsilon \beta_0$ and otherwise negative. If we change signs in each equation (20) in which the left member is negative, and then drop each non-positive η and ζ from the left (one from each equation), we are left with the inequalities

$$\Delta_{M+1, \dots, N} w'_J \leqq A^{h_J}_{1_J} \sum [h_J, k_K] A^{1_{K+1}}_{k_K} w_K. \tag{21}$$

Finally we employ lemma 2, which implies in the present case that

$$w_J \leqq [h_J, k_J] A^{k_J}_{h_J} w'_J, \tag{22}$$

and combine these inequalities with (21) to obtain

$$\Delta_{M+1, \dots, N} w_J \leqq B^J \sum [J, K] B_K w_K, \tag{23}$$

where

$$B^J \equiv A^{k_J}_{1_J}; B_K \equiv A^{1_{K+1}}_{k_K}, [J, K] = [k_J, k_K]. \tag{24}$$

(Note that the superscript J is not intended as an exponent.)

If (21) and (22) are regarded as inequalities for the determination of the w's, then (23) are the necessary and sufficient conditions for the consistency of these (cf. Dines, 1919). Likewise, by an argu-

ment which parallels that given in II, we can show that (22) and (23) are the necessary and sufficient conditions for the determination of the remaining w's in the multiple circuit. If these can be solved, then all remaining y's and z's, and hence all σ's, are obtainable as solutions of a consistent system of equations. Hence to show the necessity and the sufficiency of the conditions of the theorem, we have only to show the consistency of (23). We first suppose (23) consistent and show the necessity of the conditions of the theorem.

Now all the w's are positive, as is the Δ. The inequalities (23) can also be written in the form

$$\Delta_{M+1,\dots,N}\, w_J \leqq [1, J]\, B^J \sum [1, K]\, B_K\, w_K \tag{25}$$

where the sum is independent of J. Hence either $[1, J]B^J$ is positive for all J or negative for all J, according as the sum is positive or negative. Hence the coefficient of each w_K on the right in (25) or in (23) has the same sign in every inequality, and is the same as the sign of A_K, since this is its coefficient in the K-th inequality. Certainly there must be some K for which $A_K > 0$ if (23) are consistent. If, for some K, $\Delta_{K,M+1,\dots,N} \leqq 0$, then we have completed our first task and shown the necessity of the conditions in question. If not, then we can suppose that $A_M > 0$, and since by assumption $\Delta_{M,M+1,\dots,N} > 0$, it is legitimate to multiply the J-th inequality $(J < M)$ by $\Delta_{M,M+1,\dots,N}$, the M-th by $[J, M]B^JB_M$ and add. After suppressing the factor $\Delta_{M+1,\dots,N}$ which appears on both sides of the result, and is known to be positive, there results the system,

$$\Delta_{M,M+1,\dots,N}\, w_J \leqq B^J \sum_{K=1}^{M-1} [J, K]\, B_K\, w_K \,(J < M)\,, \tag{26}$$

of $M - 1$ inequalities independent of w_M.

The argument can be paraphrased for this system with $M - 1$ replacing M, and if every $\Delta_{K,M,\dots,N} > 0$ we obtain a similar system of $M - 1$ inequalities. Proceeding thus sequentially we either reach a stage at which there is a negative Δ, in which case the necessity of the conditions is proved, or else we continue to obtain finally the inequality

$$\Delta_{2,3,\dots,N}\, w_1 \leqq A_1\, w_1 \tag{27}$$

as the condition for the consistency of the preceding systems, and this can be satisfied only if

$$\Delta_{1,2,\dots,N} \leqq 0\,.$$

This proves the necessity of (iii) in the theorem.

To prove the sufficiency, if there are negative A_J's, let these be

the first M_1. For $M_1 < J \leqq M$, by hypothesis if we subtract the sum of all of the A_J from $\Delta_{M+1, \cdots, N}$, the result is negative, while the Δ itself is positive. Hence there must be some maximal number (possibly zero) of these A_J's, each taken once, whose sum does not exceed this Δ. Let this number be $M - M_2 \geqq 0$, and, if $M_2 < M$, let A_M, A_{M-1}, $\cdots$ be a set of the A's whose sum does not exceed the Δ. We may then proceed with our elimination from (23) until we reach a set which has the same form as (23) with M_2 replacing M. In these inequalities, when all terms are transposed to the right, the first M_1 of the w's have everywhere negative coefficients, the remaining $M_2 - M_1$ of the w's have everywhere positive coefficients. If $M_1 = 0$, the inequalities can be satisfied by taking for the w's any positive quantities. If $M_1 > 0$, the first $M_2 - 1$ of the w's can be taken as any positive quantities, after which the inequalities impose M_2 lower limits on the choice of the last. Since the compatibility of each set of inequalities is a sufficient condition for the compatibility of the preceding set, the theorem is now established for the case when α and β have no common zero.

To prove the theorem in general we note first that condition (ii) of the theorem is certainly necessary, since if any fiber j_J which is inactive for both α and β is removed from the circuit, the removal will not affect the activity of other fibers in the system. But this removal reduces to a simple chain that part of the J-th circuit which follows j_J, and its activity is thus uniquely determined by the σ's and hence the same for α and β. Therefore, since for such circuits the fiber n_J must make the same contribution to y, as to z, equations (14) are unaffected in this more general case except for the addition on the right of these contributions, equations (15) and following are unaltered, and equation (16) still holds when J refers to one of the circuits now being considered, provided there is an h_J which is a zero of one but not of the other of α and β. Thus the necessity of condition (i) of the theorem follows in the general case.

Suppose now the conditions of the theorem are satisfied and let us undertake to determine a σ consistent with α and β. First, disregarding the circuits in which α and β have a common zero, choose the σ for the remaining system as above. Note that all equations and inequalities in y, z and σ are homogeneous, so that the introduction of a common positive multiplier throughout will not affect the result. Consider any circuit, J, in which α and β are to have a common zero. By an interchange of notations, if necessary, we may suppose that $W = y_{1_J} - z_{1_J} > 0$. Then either fiber 1_J is active in both α and β, inactive in both, or else active in α, inactive in β. Since the α and β are both admissible, the one case or another can hold only when the

threshold of 1_J satisfies certain inequalities in terms of the thresholds of the other fibers 1_K, which inequalities, in fact, limit initially the set of AP's α and β which are to be classed as admissible. But since these hold, and since

$$y_{1_J} - y_{1_K} = h_{1_K} - h_{1_J} = z_{1_J} - z_{1_K},$$

K referring to a circuit for which the σ's have already been chosen and since, finally, the introduction of a positive factor into the y's, z's and σ's already chosen will not affect the final result, we may always adjust this positive factor so that y_{1_J} and z_{1_J} have the desired signs, and 1_J will thus be made active or inactive, as the case may be, for each of α and β. But this being done, α_0 and β_0 having the prescribed evenness and oddness, each successive σ in the circuit can then be chosen in turn to satisfy the requirements as to the activity or inactivity of the corresponding fiber, after which, if n_J is to be made active, the value of S_1 must be increased or decreased, as the case may be, in an amount sufficient to cancel the contribution (the same with α as with β) of this fiber. Thus the theorem is proved in complete generality.

The author is indebted to Dr. Alvin M. Weinberg for helpful suggestions and criticisms on this and the preceding papers in this series.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

LITERATURE

Dines, Lloyd L. 1919. "Systems of Linear Inequalities." *Annals of Mathematics* (2) **20**, 191-199.

Householder, A. S. 1941. "A Theory of Steady-State Activity in Nerve-Fiber Networks: I. Definitions and Preliminary Lemmas." *Bull. Math. Biophysics*, **3**, 63-70.

Householder, A. S. 1941. "A Theory of Steady-State Activity in Nerve-Fiber Networks: II. The Simple Circuit." *Bull. Math. Biophysics*, **3**, 105-112.

Householder, A. S. 1941. "A Theory of Steady-State Activity in Nerve-Fiber Networks: III. The Simple Circuit in Complete Activity." *Bull. Math. Biophysics*, **3**, 137-140.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

A KINETIC THEORY OF DIFFUSION FORCES IN METABOLIZING SYSTEMS

H. D. LANDAHL
THE UNIVERSITY OF CHICAGO

The development of a molecular theory of the diffusion drag forces in liquids is attempted by considering the liquids as limiting cases of very dense gases. An expression is derived for the force on a small particle suspended in a nonuniform mixture of such gases on the basis of kinetic theory. Another expression for the order of magnitude of the force on a larger particle is obtained by introducing certain hydrodynamical considerations. These results are compared with an expression previously derived by N. Rashevsky, and estimates are made of the order of magnitude of the volume force on the granules and particles within a typical cell due to the diffusion of metabolites. It is found that the drag forces, exerted by a diffusing solute, depend to a very large extent on the physical properties of the solvent.

The drag forces exerted by a diffusing substance must be considered in a complete theory of metabolizing systems. It has been suggested that they may play an important role in cell division and other phenomena (Rashevsky, 1938). An expression for the force on a particle due to a diffusing substance was derived by N. Rashevsky on the basis of asymmetric molecular bombardments. A corresponding expression was derived by G. Young (1938) on the basis of a hydrodynamical treatment. In the former treatment the effect of the solvent was not adequately accounted for, while in the latter, it was neglected. It is the purpose here to derive a more complete expression on the basis of the kinetic theory of gases.

We shall consider the solvent and solute as non-uniform dense gases diffusing through each other in the presence of another kind of solute molecules, having only thermal motion. If the stationary solute is sufficiently dilute, interactions between these molecules may be neglected, and we may consider the force on each molecule separately. Thus for convenience we shall consider only one such molecule, and, in order to distinguish it from the other molecules we shall refer to it as the particle. The molecules of the solvent will be referred to as class 1, and the parameters for these molecules will bear the subscript 1. Similarly the solute molecules will be referred to as class 2, while the subscript 3 will refer to the particle.

Let N_1 be the molecular density of molecules 1 of mass m_1 and

diameter σ_1, for which the most probable thermal speed is $\alpha_1 = \sqrt{2kT/m_1}$. A similar notation will be used for molecules of class 2, and for the particle, except that N is not defined for the particle. Let $\mathbf{c}_i$ be the velocity of a particular member of class i before, and $\mathbf{c}'_i$ the velocity after collision. The molecules of all classes are assumed to be elastic spheres.

Since we intend to extrapolate any results to liquids, we wish to consider the effects due to the finite sizes of the molecules. The first approximation, f_1^0, to the distribution function of the velocities of class 1 molecules, f_1, is given by the Maxwell distribution. An equation, whose solution gives a second approximation to $f_1 = f_1^0 + f_1^1$ for a mixture of two dense gases, is given by S. Chapman and T. G. Cowling (1939). Similarly, equations for collision frequency are given, so that one may obtain the average change in velocity of the particle. The presence of a third type of particle introduces a further complication. We shall not attempt this general type of approach, but use a procedure in which the effect of molecular size will be considered in connection with collision frequency, but neglected in connection with the second approximation to the distribution function, f_1. The effect of the size of the particle on the distribution function will be similarly neglected. If only the particle size were to be considered, one might treat its effect on the distribution function as done by P. C. Epstein (1924) in obtaining Stoke's law. The distribution functions will be considered as independent of position and the effect of position will be brought in as is frequently done in this type of problem.

The number of molecules per unit volume having velocities in the element, $d\mathbf{c}$, of velocity space, is $Nfd\mathbf{c}$. Then f_1, the distribution function for a class 1 molecule, is given by

$$f_1 = \pi^{-3/2}\,\alpha_1^{-3}\,e^{-\frac{(\mathbf{c}_1-\omega)^2}{\alpha_1^2}}, \tag{1}$$

where ω is the mass velocity of the mixture. A similar expression holds for class 2 molecules. For the particle we have

$$f_3 = \pi^{-3/2}\,\alpha_3^{-3}\,e^{-\frac{c_1^2}{\alpha_3^2}}, \tag{2}$$

as we consider the particles to have only thermal motion.

Consider a collision between a molecule of class 1 and the particle. Let $\mathbf{k}$ be a unit vector from the center of the particle through the center of the molecule 1. The change in velocity of the particle is given by the expression (Chapman and Cowling, 1939, p. 58)

$$\mathbf{c}'_3 - \mathbf{c}_3 = -\frac{2m_1}{m_1 + m_3}(\mathbf{c}_{31}\cdot\mathbf{k})\mathbf{k}, \tag{3}$$

$$\mathbf{c}_{31} = \mathbf{c}_3 - \mathbf{c}_1 = -\mathbf{c}_{13} . \tag{4}$$

If dk represents an element of surface on a sphere of unit radius containing the point $\mathbf{k}$, then the probable number of collisions per second of molecules of velocity $\mathbf{c}_1$ with the particle, such that $\mathbf{k}$ lies in the range dk, is given by

$$\chi_{31} N_1 \sigma_{31}^2 (\mathbf{c}_{31} \cdot \mathbf{k}) dk , \tag{5}$$

$$\sigma_{31} = (\sigma_3 + \sigma_1)/2 , \tag{6}$$

where χ_{31} is a factor depending on the density of the particles, its value being unity for rarified gases (Chapman and Cowling, 1939, p. 292), and where N_1 is evaluated at the position of molecule 1 at its last collision with any molecule of either class 1 or 2. The net acceleration of the particle is the average change in velocity per unit time, or the integral of the expression obtained by multiplying the factors from (1), (2), (3) and (5). Multiplying the acceleration by the mass, m_3, we obtain $\mathbf{F}_{31}$ as the force on the particle due to bombardments of class 1 molecules where

$$\mathbf{F}_{31} = -\frac{2m_1 m_3 \sigma_{31}^2}{m_1 + m_3} \int\int\int \chi_{31} N_1 (\mathbf{c}_{31} \cdot \mathbf{k})^2 f_1 f_3 \mathbf{k} dk d\mathbf{c}_1 \, d\mathbf{c}_3 . \tag{7}$$

The value of N_1 is given by

$$N_1 = N_{10} + (\sigma_{31}\mathbf{k} - L_{12}\mathbf{c}_1/c_1) \cdot \operatorname{grad} N_{10} , \tag{8}$$

since N_1 is taken at the point of last collision. The quantity L_{12} is the mean free path of molecule 1 in the mixture of 1 and 2 molecules. We shall use the expression corrected for persistence of velocity (Jeans, 1940, p. 206) in which the χ factors have been introduced and in which the coefficient α_{12} is taken equal to 0.2 and $\theta = 0.4$. Then

$$L_{12} = \frac{\sqrt{m_1 + m_2}}{1.2\, \pi \sigma_{12}^2 N_{20} \chi_{12} \sqrt{m_2} + .6\sqrt{2}\, \pi \sigma_1^2 N_{10} \chi_{11} \sqrt{m_1 + m_2}} . \tag{9}$$

The values N_{10} and N_{20} are the values which N_1 and N_2 would take at the center of the particle if the latter were absent. Expressions similar to (6), (7), (8) and (9) may be obtained for collisions of molecules of class 2 with the particle by interchanging the subscripts 1 and 2.

The factor χ_{31} depends upon the number densities N_1 and N_2 in general, and upon σ_1 and σ_2 as well as upon σ_3. To a first approximation we may write

$$\chi_{31} = \chi_3 + a_1 N_1 + b_1 N_2 . \tag{10}$$

The value of χ_3 is unity if the effect of the particle is neglected, otherwise it is greater than one. The factor χ_{31} is to be evaluated at $\frac{1}{2}\sigma_{13}\mathbf{k}$, the point between centers at collision.

Introducing (1), (2) and (8) into (7), and defining ν_1 as a unit vector in the direction of the gradient of N_1, we obtain for the expression under the integral, where $\omega = \omega_1 \nu_1$:

$$\begin{aligned}
&\frac{N_1 \chi_{31}}{\pi^3 \alpha_1^3 \alpha_3^3} \iiint e^{-\frac{c_1^2}{\alpha_1^2}} e^{-\frac{c_3^2}{\alpha_3^2}} (\mathbf{c}_{31} \cdot \mathbf{k})^2 \mathbf{k} dk d\mathbf{c}_1 \, d\mathbf{c}_3 + \frac{2N_1 \omega_1 \chi_{31}}{\pi^3 \alpha_1^5 \alpha_3^3} \\
&\quad \times \iiint e^{-\frac{c_1^2}{\alpha_1^2}} e^{-\frac{c_3^2}{\alpha_3^2}} (\mathbf{c}_1 \cdot \nu_1)(\mathbf{c}_{31} \cdot \mathbf{k})^2 \mathbf{k} dk d\mathbf{c}_1 \, d\mathbf{c}_3 \\
&+ \frac{(\chi_{31} + .5a_1 N_1 - 5b_1 N_1)}{\pi^3 \alpha_1^3 \alpha_3^3} \sigma_{31} \frac{\partial N_1}{\partial \nu_1} \iiint e^{-\frac{c_1^2}{\alpha_1^2}} e^{-\frac{c_3^2}{\alpha_3^2}} \\
&\quad (\mathbf{k} \cdot \nu_1)(\mathbf{c}_{31} \cdot \mathbf{k})^2 \mathbf{k} dk d\mathbf{c}_1 \, d\mathbf{c}_3 - \frac{\chi_{31} L_{12}}{\pi^3 \alpha_1^3 \alpha_3^3} \frac{\partial N_1}{\partial \nu_1} \\
&\quad \times \iiint e^{-\frac{c_1^2}{\alpha_1^2}} e^{-\frac{c_3^2}{\alpha_3^2}} \frac{(\mathbf{c}_1 \cdot \nu_1)}{c_1} (\mathbf{c}_{31} \cdot \mathbf{k})^2 \mathbf{k} dk d\mathbf{c}_1 \, d\mathbf{c}_3 .
\end{aligned} \tag{11}$$

In the above expression only terms in the first power of the gradient of N_1 are retained. The mass velocity is considered due only to diffusion and hence is proportional to $\partial N_1/\partial \nu_1 = \partial N_2/\partial \nu_2$. For it we shall use the expression given by Loeb (1934, p. 263), using somewhat different notations, but in which L_{12} is given by (9) above:

$$\omega_1 = \frac{2}{3\sqrt{\pi}(N_1 + N_2)} (\sigma_1 L_{12} - \sigma_2 L_{21}) \frac{\partial N_1}{\partial \nu_1}. \tag{12}$$

The second term arises from the first term of the expansion of (1), since $\omega_1 << \alpha_1$. The subscript o has been dropped so that χ_{31}, N_1 and N_2 hereafter are to be taken at the center of the particle.

From consideration of symmetry, we can see that the net force must lie in the direction of the gradient. Thus $\mathbf{F}_{31} \cdot \nu_1$ is the value desired and the force is then with reference to the direction ν_1. We thus take the component of each term of (11) in the direction ν_1. The integration with respect to dk may be simplified by the substitutions:

$$l = (\mathbf{k} \cdot \mathbf{c}_{31})/c_{31}, \cos\beta = (\mathbf{c}_{31} \cdot \nu_1)/c_{31}, m = \mathbf{k} \cdot \mathbf{q},$$

where

$$\mathbf{q} = csc\,\beta(\nu_1 - \cos\beta\, \mathbf{c}_{31}/c_{31}), dk = dl dm/\sqrt{1 - m^2 - l^2},$$

$$(\mathbf{k} \cdot \nu_1) = m \sin\beta + l \cos\beta .$$

The integration with respect to l is carried out from 0 to $\sqrt{1-m^2}$ as the angle, $\cos^{-1} l$, must lie between 0 and $\pi/2$ for a collision to be possible, while m is integrated from -1 to 1. The integration covers two of the four quadrants so that because of symmetry the result must be doubled. For the integration with respect to the velocity elements, a linear transformation of the velocity components may be used (Loeb, 1934, p. 551).

The first integral of (11) vanishes as would be expected, since it does not depend upon the gradient, and is essentially the resultant force on a particle in a uniform gas without mass motion. The value of the integral in the second term of (11) is

$$-2/3\,\pi^{7/2}\,\alpha_1^6\,\alpha_3^3\,\sqrt{m_1+m_3}/\sqrt{m_3}$$

so that the complete term becomes

$$\frac{8\pi^{\frac{1}{2}}\,m_1\,\sqrt{m_3}}{3\sqrt{m_1+m_3}}\,\chi_{31}\,N_1\,\sigma_{31}^2\,\alpha_1\,\omega_1. \tag{13}$$

The integral in the third term of (11) becomes

$$\pi^4\,\alpha_1^5\,\sigma_3^3\,(m_1+m_3)/3m_3$$

so that the complete term becomes

$$-\frac{4}{3}\pi\,kT\,(\chi_{31}+.5a_1N_1-.5b_1N_1)\,\sigma_{31}^3\,\frac{\partial N_1}{\partial \nu_1}. \tag{14}$$

The integral of the last term of (11) was not successfully evaluated. Hence two special cases were considered—one in which α_1 is negligible compared with α_3, and one in which α_3 is negligible compared with α_1. In the former case, the integral vanished. In the latter, in which the thermal motion is negligible, we obtain for the complete term

$$-\frac{\pi\,kTm_3}{m_1+m_3}\,\chi_{31}\,L_{12}\,\sigma_{31}^2\,\frac{\partial N_1}{\partial \nu_1}. \tag{15}$$

Thus the desired expression must reduce to (15) for large m_3 but must vanish for $m_3 = 0$ even when the factor $m_3/(m_1+m_3)$ is removed. Hence the expression will generally contain m_1 and m_3 and may be written approximately in the form

$$-\frac{\pi\,kTm_3^s}{(m_1+m_3)^s}\,\chi_{31}\,L_{12}\,\sigma_{31}^2\,\frac{\partial N_1}{\partial \nu_1}, \tag{16}$$

where $s > 1$.

The net force F_{31}, in the direction ν_1, is then given by the sum of the terms (13), (14) and (16), or introducing the expressions for ω_1 and L_{12} we have

$$
\begin{aligned}
F_{31} = {} & \frac{160}{27\pi}\sqrt{\frac{m_1 m_3 (m_1 + m_2)}{m_1 + m_3}}\,\frac{kT\,\chi_{31}\,N_1\,\sigma_{31}^2}{N_1 + N_2} \\
& \times\left[\frac{1}{\sqrt{2}\sigma_1^2 N_1 \chi_{11}\sqrt{m_1(m_1+m_2)} + 2\sigma_{12}^2 N_2 \chi_{12}\sqrt{m_1 m_2}}\right. \\
& \left. - \frac{1}{\sqrt{2}\sigma_2^2 N_2 \chi_{22}\sqrt{m_2(m_1+m_2)} + 2\sigma_{12}^2 N_1 \chi_{21}\sqrt{m_1 m_2}}\right]\frac{\partial N_1}{\partial \nu_1} \\
& - \frac{4}{3}\pi\, kT(\chi_{31} + .5a_1 N_1 - .5b_1 N_1)\,\sigma_{31}^3\,\frac{\partial N_1}{\partial \nu_1} \\
& - \frac{5kTm_3^3\sqrt{m_1 + m_2}\,\chi_{31}\,\sigma_{31}^2}{3(m_1+m_3)^3\sqrt{2}\sigma_1^2 N_1 \chi_{11}\sqrt{m_1+m_2} + 2\sigma_{12}^2 N_2 \chi_{12}\sqrt{m_2})}\,\frac{\partial N_1}{\partial \nu_1}
\end{aligned}
\tag{17}
$$

In the present development we are considering the mass velocity as due to diffusion only. In general, there may be a mass motion which does not vanish with diffusion. If this component is included, and the gradients vanish, then the resulting expression gives the force on a particle moving relative to the solvent. If $m_3 >> m_1$ and $\sigma_3 >> \sigma_{12}$ and $\chi_{31} = 1$, this reduces to the expression obtained by P. S. Epstein (1924, p. 720) and M. Smoluchowski (1906) for the force on a smooth particle which is small compared with the mean free path.

The force on the particle due to molecules of class 2 in the direction of the gradient of N_2 is given by an expression similar to (17) in which subscripts 1 and 2 are interchanged. The net force due to both types of molecules in the direction of the gradient of N_2 is given by $F_{32} - F_{31}$. We shall be especially interested in the case in which N_1 (solvent) is considerably larger than N_2 (solute) and in which m_3 is considerably larger than m_2 or m_1, where generally $m_2 > m_1$. Now $\chi_{12} = \chi_{21}$ (Chapman and Cowling, 1939, p. 292) and χ_{11} because of the above restrictions is approximately equal to χ_{12}. The coefficient a_1 gives the amount by which a single class 1 molecule increases collision frequency between a class 1 molecule and the particle. This is of the order of the volume of the molecule, or because the molecular density is of the order of unity, we shall set $a_1 = m_1$, and similarly $a_2 = m_2$. The effect of a class 2 molecule on collisions between class 1 molecules and the particle is in general a more complex function, but again the effect per molecule, b_1, is of the order of m_2, at least if the particle is not too much larger than the molecules. We shall thus set $b_1 = m_2$

and similarly $b_2 = m_1$. Then $\chi_{31} = \chi_{32}$. Under these assumptions we have for the net force $F_3 = F_{32} - F_{31}$,

$$F_3 = -\frac{kT\,\chi_{31}\,\sigma_3^2}{24\chi_{11}\,N_1\,\sigma_1^2}\left[(\sqrt{m_2} - 1.12\sqrt{m_1})\,\frac{\sigma_1^2}{\sigma_{12}^2}\sqrt{\frac{m_1 + m_2}{m_1\,m_2}}\right.$$
$$\left. + .16\right]\frac{\partial N_2}{\partial \nu_2} - \frac{kT\,\sigma_3^2}{3}\left[\frac{3}{2}\chi_{31}(\sigma_2 - \sigma_1) + (m_2 - m_1)\,\sigma_3\,N_1\right]\frac{\partial N_2}{\partial \nu_2}. \tag{18}$$

If, in particular, the molecular diameters of molecules 1 and 2 are proportional to the masses, one can show that for $m_2 > m_1$, and $\sigma_2 > \sigma_1$, F_3 is negative, while for $m_1 > m_2$, $\sigma_1 > \sigma_2$, F_3 is positive. In general, this may not be so. However, from the above equation, one would expect a net outward force on particles in a volume element for which the divergence of the gradient of solute concentration, m_2N_2, is negative (the solute being produced in the element) provided the solute molecules are larger than the solvent molecules; but one would expect an inward force on particles in the element if the solute is being produced, if they are smaller than the solvent molecules. This result is of interest in the diffusion force theory of cell division (Rashevsky, 1940).

The importance of the molecular properties of the molecules in determining the force is brought out in (18). It is also clear that the effect of the size of the molecules and particle becomes important as the density rises, especially since we wish the effect of the difference of two net forces. It might be pointed out that the viscosity of carbon dioxide was predicted for a range of values including some in the liquid state, suggesting that in liquids the momentum transport mechanism is similar to that in gases (Chapman and Cowling, 1939, p. 209). For a complex liquid like water, such a generalization is more doubtful.

We have considered the molecules as if they were smooth elastic spheres. If one considered various types of forces of interaction, different results would be obtained. In general, the result in such cases is very similar to the simplified case. If only numerical factors of the order of unity were involved, we would neglect them. But, since we are dealing with differences, and the factors might not be the same in the two opposing forces, it would be well to investigate under what conditions the results would materially differ from the present case.

Thus far we have had to restrict the diameter of the particle to values less than the mean free paths L_{12} and L_{21}. If the particle is much larger than the mean free paths, we may treat the solvent and solute as fluids flowing through each other. G. Young (1940) points out that in such a case the force due to the moving fluids is the sum

of the forces exerted by each fluid acting independently. If v_1 and v_2 are the velocities of solvent and solute due to interdiffusion, the particle being at rest, the force on the particle due to the solvent and solute are given by Stoke's law

$$\mathbf{F}_{31} = 3\,\pi\,\eta_1\,\sigma_3\,\mathbf{v}_1\,, \tag{19}$$

$$\mathbf{F}_{32} = 3\,\pi\,\eta_2\,\sigma_3\,\mathbf{v}_2\,. \tag{20}$$

The viscosity η_2 is taken to be that which the solute would have if it were a gas at the same temperature and density. The viscosity η_1 has a similar meaning, but as we shall consider the case in which $N_1 >> N_2$, we may also refer to η_1 as the solvent viscosity.

The rate of mass transport, $d(m_1\,N_1)/dt$, across a unit area is proportional to the gradient of the mass density and in the opposite direction. The proportionality constant is the diffusion coefficient D_{12} of the mixture. But this flow is just the velocity times the mass density. Thus

$$N_1\,\mathbf{v}_1 = -\,D_{12}\,\frac{\partial\,N_1}{\partial\,\nu_1}\,v_1\,, \tag{21}$$

and a similar expression for the solute. The net force $\mathbf{F}_3$ is then, assuming $N_1 + N_2$ is a constant,

$$\mathbf{F}_3 = 3\,\pi\,\sigma_3\,D_{12}\left[\frac{\eta_2}{N_2} - \frac{\eta_1}{N_1}\right]v_2\,. \tag{22}$$

The expression for the diffusion coefficient as given by Einstein holds roughly for molecules, thus we may write approximately

$$D_{12} = \frac{kT}{3\pi\,\eta_1\,\sigma_2}. \tag{23}$$

The expression for viscosity of a gas is

$$\eta = \frac{2\,\psi\,\sqrt{kTm}}{3\,\pi^{3/2}\,\sigma^2}, \tag{24}$$

where ψ is a factor introduced for dense gases, arising for the same reasons as χ. The viscosity of a dense gas is only slightly different from a rarified gas until the pressure is raised to many atmospheres. In the case of carbon dioxide, in which Enskog predicted the viscosity into the liquid state (Chapman and Cowling, 1939, p. 289), the range of variation is only about five. In the case of water, the range is much greater, being of the order of one hundred, indicating that other factors may enter, even considering the aggregation of molecules. For the sake of analogy, we may write the solvent viscosity in this form.

Making use of expressions (23) and (24), we obtain an expression for the force in the direction of the gradient of N_2:

$$F_3 = \frac{kT\,\sigma_1^2\,\sigma_3}{\sigma_2\sqrt{m_1}}\left[\frac{\psi_2\sqrt{m_2}}{\psi_1 N_2\,\sigma_2^2} - \frac{\sqrt{m_1}}{N_1\,\sigma_1^2}\right]\frac{\partial N_2}{\partial \nu_2}. \tag{25}$$

We are interested in the special case in which $N_1 >> N_2$. If then N_1/ψ_1 is sufficiently greater than N_2/ψ_2, we have approximately

$$F_3 = -\frac{\psi_2\,kT\,\sigma_1^2\sqrt{m_2}\,\sigma_3}{\psi_1\,\sigma_2^3\sqrt{m_1}\,N_2}\,\frac{\partial N_2}{\partial \nu_2}. \tag{26}$$

On the other hand for large enough N_2, the sign of the force is reversed, and the expression for the force is approximately

$$F_3 = \frac{kT\,\sigma_3}{\sigma_2 N_1}\,\frac{\partial N_2}{\partial \nu_2}. \tag{27}$$

As we wish to consider the case in which $N_1 >> N_2$, the solute would not be a particularly dense gas, so that continuing to neglect the effect of interaction, $\psi_2 = 1$. If the molecular densities are approximately the same for solvent and solute, equation (26) becomes

$$F_3 = -\frac{kTm_1^{1/6}}{\sqrt{m_2}\,\psi_1}\,\frac{\sigma_3}{N_2}\,\frac{\partial N_2}{\partial \nu_2}. \tag{28}$$

Comparing equations (26) and (18) one notes that in (26) the force varies only as the linear dimensions of the particle and depends on the gradient of the logarithm of the concentration, whereas in (18) the force varies with the square of the particle diameter, and with the gradient of the concentration. Also the force as given by (26) does not change sign when $m_2 < m_1$, $\sigma_2 < \sigma_1$. But from (25), if $m_2 << m_1$, and $\sigma_2 << \sigma_1$ and N_2 is not too much larger than N_1, the sign of the force may change.

There are several reasons for the difference in form of the equations (18) and (26). In the kinetic theory treatment we consider that σ_3 is smaller than the mean free path, while in the second treatment, the assumption is made that σ_3 is considerably greater than the mean free path so that the fluid may be considered as continuous. This is just the reason for the difference in exponent of σ_3 as is discussed by P. S. Epstein (1924). The other basic type of difference is that of the appearance of the gradient of the logarithm of N_2 in (25). But it should be noted in the more general expression, from which (18) arises, N_2 does appear in the denominator. Furthermore, if instead of

the expression (9) for L_{12}, we use that value obtained by ignoring collisions of like molecules (cf. Stefan and Maxwell mass velocity, Loeb, 1934, p. 266), a term involving the gradient of the logarithm arises. As has been mentioned previously, the term in (18) containing the cube of the diameter is doubtful. On the other hand, in the derivation of (26) it was assumed that the viscosity, η_2, of the solute has the value it would have if it were a gas at the same temperature and density.

In N. Rashevsky's derivation of the diffusion drag force on a particle of volume V_p, he obtained an expression,

$$F = -\frac{3RT}{2M} \alpha V_p \operatorname{grad} c,$$

by considering a continuous pressure function due to molecular bombardments of a solute of molecular weight, M, and integrating over the surface of the particle to obtain the net force (cf. Rashevsky, 1938, chap. vii). The force on a molecule of the solvent was considered in a similar manner. He calculated the non-homogeneity of the solvent produced by this force, and showed that this nonuniformity results in a force on the particle in the opposite direction to the force due to the solute. Thus the above expression was obtained for the total force on the particle. However, in considering the solvent molecules as particles of sufficient size to consider a continuous pressure function, the opposing force due to the solvent was underestimated and the above α, instead of being about 0.7, becomes practically zero. Since some work has been done on the basis of that expression, it would be well to compare the order of magnitude of the net volume force on many particles which comprise a certain fraction, μ, of the solution, for biologically plausible values. In both cases, the net volume force is proportional to the gradient. The coefficient of the grad c from Rashevsky's equation is of the order of 10^7 for $\mu = .1$, $V_p \backsim \sigma_3^3 \backsim 10^{-18}$, $M \backsim 10^2$. Using corresponding values in the corresponding expression from (18), together with values which follow from identifying the solvent with water, one finds the same order of magnitude for the coefficient of the grad c, $c = m_2 N_2$. The second term in (18) is found to be largest for these values. But this term is that remaining from the original terms due to the finite size of the particle, and is uncertain, since the treatment of the size of the particle and molecules was not at all complete. If this term was neglected, the resulting coefficient of grad c would be of the order of 10^2 to 10^4 instead of 10^7, depending on the value of σ_3 as it varies in the range from 10^{-5} to 10^{-7} centimeters, thus materially reducing the magnitude of the force.

In the theory of forces in cell division, we are particularly interested in forces on particles in the range 10^{-7} to 10^{-5} cm. We shall estimate the order of magnitude of the force per cubic centimeter containing a number of particles which take up a fraction, μ, of the unit volume. Taking the fairly plausible values: $m_1 = 6 \times 10^{-23}$ gm., $m_2 = 2 \times 10^{-22}$ gm., $\mu = .1$, $N_1 = 10^{22}$, $N_2 = 10^{19}$, $(\partial N_2/\partial r_2) = 10^{21}$, we have for the volume force from equation (26) on particles of sizes 10^{-7}, 10^{-6}, and 10^{-5} cm. the respective values 10^8, 10^6 and 10^4 dynes cm^{-3}. Similarly from equation (18) we obtain the corresponding forces per unit volume: 6×10^7, 3×10^7, and 3×10^7 dynes cm^{-3}. The contributions from the first term of (18) are 10^6, 10^5 and 10^4 respectively while those due to the second term of (18) are each 3×10^7 dynes cm^{-3}. In view of the previous discussion, the latter term is uncertain. In any case, the order of magnitude of the force per unit volume turns out to be of the order of magnitude of 10^4 to 10^7 dynes cm^{-3}. Using the above values for μ, M and for the gradient in the expression derived by N. Rashevsky (1940, chap. iii), one obtains for the force per unit volume a value about 10^7 dynes cm.$^{-3}$, which is of the same order of magnitude or greater than that obtained above. Some of these estimates of the volume force are considerably lower than previously given, but we shall see in a paper to be published subsequently that a lower estimate is still adequate. It will be noted that the discrepancy between the first and second terms of (18) is smaller when forces per unit volume are considered than when the coefficients of the concentration gradient are compared.

Summary. An expression has been derived for the force on a particle in a non-uniform mixture of gases. The size of the molecules and particle has been taken into account only in an approximate manner. An attempt is made to extrapolate the results to liquids, and using biologically plausible values for the various parameters, the force on particles in a unit volume is estimated. A similar expression for the force on a particle is obtained on hydrodynamic grounds and the latter expression is compared with the former. A similar estimate of the force per unit volume is made. The two estimates are of about the same order of magnitude. These results are also compared with the expression obtained by N. Rashevsky. Although his treatment was not adequate, the order of magnitude of the force per unit volume comes out about the same. Thus subsequent work based on his equation, especially in the problem of cell division are probably not basically affected.

The author is indebted to Dr. N. Rashevsky for suggesting the problem and to Dr. A. S. Householder for checking the calculations.

LITERATURE

Chapman, S. and T. G. Cowling. 1939. *The Mathematical Theory of Non-Uniform Gases.* Cambridge: The University Press.

Epstein, P. S. 1924. "On the Resistance Experienced by Spheres in Their Motion Through Gases." *Phys. Rev.* **23**, 710-733.

Jeans, J. J. 1940. *An Introduction to the Kinetic Theory of Gases.* Cambridge: The University Press.

Loeb, L. B. 1934. *The Kinetic Theory of Gases.* New York and London: The McGraw-Hill Book Company.

Rashevsky, N. 1938. *Mathematical Biophysics. Physico-mathematical Foundations of Biology.* Chicago: The University of Chicago Press.

Rashevsky, N. 1940. *Advances and Applications of Mathematical Biology.* Chicago: The University of Chicago Press.

Smoluchowski, M. 1906. "Zur kinetischen Theorie der Brownschen Molecularbewegung und der Suspensionen." *Ann. d. Phys.* **21**, 756-780.

Young, G. 1938. "Theory of Diffusion Forces in Metabolizing Systems." *Growth,* **2**, 165-180.

Young, G. 1940. "Some General Theorems on the Motion of Incompressible Viscous Fluids." *Bull. Math. Biophysics,* **2**, 145-155.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

SUGGESTIONS FOR A MATHEMATICAL BIOPHYSICS OF AUDITORY PERCEPTION WITH SPECIAL REFERENCE TO THE THEORY OF AESTHETIC RATINGS OF COMBINATIONS OF MUSICAL TONES

N. RASHEVSKY
THE UNIVERSITY OF CHICAGO

Generalising the previously studied neurobiophysical schemes, consisting of excitatory and inhibitory elements, a neural mechanism is discussed, which may be involved in the perception of combinations of musical tones. Equations, giving the total value of central excitation for a combination of any two tones are derived, available observations are discussed in the light of the suggested theory.

Since the appearance of the classical work of H. Helmholtz (1862), a considerable number of mathematical studies have been contributed to the fields of auditory perception (Waetzman, 1912; 1926). All these studies confined themselves principally to the mechanism of the peripheral organ. Although even under those restricted conditions a remarkable amount of success has been achieved, it is doubtful whether a complete theory cannot avoid considering the phenomena involved in the central nervous system. The purpose of this paper is to make a step in that direction. Although we need not commit ourselves to any definite assumption about the functioning of the peripheral organs, we shall for convenience put ourselves on the point of view of the resonance theory of hearing. This suggests immediately the picture, that sounds of different pitch are perceived by different groups of central neurons, each group excited by one or a few adjacent fibers of the basilar membrane.

The non-linear character of the vibrating structure of the ear results in the production of harmonics even when the ear is stimulated by a pure tone, therefore any tone results in the excitation of a number of distinct neuronic groups, each corresponding to the harmonic of the tone. Thus a musical tone results in the excitation of n neuronic groups, where n is the number of harmonics which correspond to the given tone. Theoretically n may be infinite. Practically it is always limited, for very high harmonics are of subthreshold intensities. The upper limit of pitch which can be heard is also a limiting factor. In general, n may be different for different fundamental tones. For sim-

plicity we shall consider here the abstract case, where n is the same for all tones. In view of what has just been said about the non-linearity of the peripheral organ, n is not necessarily determined by the tone producing instrument. It might even be completely determined by the peripheral organ and the properties of the corresponding part of the central nervous system. The number n may vary with the pitch of the tone. Let us, however, first consider the case, that n does not depend on the pitch.

Let two tones of different pitch be presented simultaneously. Let the ratio of their fundamental frequencies be p/q, where p and q are integers and $q < p < 2q$. The total number of neuronic groups corresponding to the two tones is not equal to $2n$, because some of the groups are common to both tones. The lower tone of frequency ν covers a range of frequencies $\nu, 2\nu \cdots i\nu \cdots n\nu$. The higher tone covers the range $(p/q)\nu$, $2(p/q)\nu \cdots$, $i(p/q)\nu \cdots$, $n(p/q)\nu$. Of the n harmonics of the higher tone, those for which $i(p/q) > n$ fall outside of the range of frequencies of the lower tone. Their number is equal to $n - (q/p)n = n(p-q)/p$. Hence only the number $n - n(p-q)/p = nq/p$ of all the harmonics of the higher tone falls within the range of the frequencies corresponding to the lower tone. But every q-th harmonics of the lower pitched tone coincides with every p-th harmonics of the higher one. Hence $1/q$ of all the harmonics of the higher tone, which fall in the range of frequencies $\nu - n\nu$, are included amongst the harmonics of the lower. Thus the total number n' of neuronic centers, corresponding to two simultaneous tones is

$$n' = 2n - \frac{1}{q} \times \frac{q}{p} \times n = \frac{2p-1}{p} n . \tag{1}$$

Denoting

$$\frac{2p-1}{p} = x , \tag{2}$$

We find the following values of x for different musical intervals

	$\frac{p}{q}$	x		$\frac{p}{q}$	x
1. Minor second	$\frac{16}{15}$	1·9375.	4. Major third	$\frac{5}{4}$	1·80 .
2. Major second	$\frac{9}{8}$	1·8889.	5. Perfect fourth	$\frac{4}{3}$	1·75 .
3. Minor third	$\frac{6}{5}$	1·8333.	6. Tritone	$\frac{45}{32}$	1·9778.

7. Perfect fifth	$\frac{3}{2}$	1·6667.	10. Minor seventh	$\frac{16}{9}$	1·9375.
8. Minor sixth	$\frac{8}{5}$	1·895 .	11. Major seventh	$\frac{15}{8}$	1·9333.
9. Major sixth	$\frac{5}{3}$	1·80 .	12. Octave	$\frac{2}{1}$	1·5 .

If we consider that each neuronic center sends inhibitory fibers to all others, then the total net excitation of all the n' centers may be calculated, provided the intensities of excitation of all the groups are known. Since at this stage we are discussing the problem purely theoretically, *in abstracto,* we shall consider here a particularly simple case, in which all those intensities are equal. This at first seems to be a rather artificial assumption. It may be remarked, however, that such a situation will occur if the neurons, leading to the center in question reach their limiting excitatory values (Rashevsky, 1938, chap. xxii) at rather small intensities of the peripheral stimuli. Under these conditions, for a very wide range of stimuli, the excitation of the n' centers will remain the same. If the intensity of excitation of such a center is I, then since it receives $(n' - 1)$ inhibitory fibers from other centers, its net excitation is: $I - b(n' - 1)I$, where b is is a constant. Hence the total net excitation is of the form:

$$E = A'[n' - b(n' - 1)n' + C'] , \tag{3}$$

where A' and C' are constants, the constant C' representing a possible constant general excitatory $(C' > 0)$ or inhibitory $(C' < 0)$ level, present at the centers, and A' is always positive, being proportional to I. Because of equations (1) and (2), equation (3) may be written:

$$E = A'\{xn - b(xn - 1)xn + C'\}. \tag{4}$$

The right side of equation (4) considered now as a function of x is a parabola having a maximum for a certain x. Considering that both n and $n' = xn$ are much greater than 1, we may write equation (4) as follows:

$$E = A(x - Bx^2 + C) \tag{5}$$

where

$$A = A'n; \quad B = bn; \quad C = \frac{C'}{n} . \tag{6}$$

For each interval, characterized by given x, we can compute E. Setting the latter as has been done before (Rashevsky, 1940) propor-

tional to the aesthetic satisfaction, derived from the perception of the musical interval, we thus may estimate the value of this satisfaction and compare it with available rank order measurements.

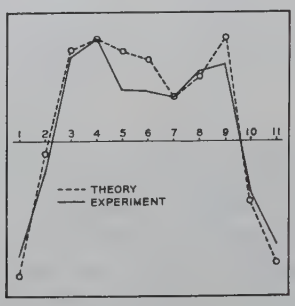

FIGURE 1

Equation (5) shows that E has a maximum for $x = x_m = 1/2B$. Experimentally observed rank order values of the pleasantness of simultaneously sounded musical intervals (Valentine, 1913) indicate a maximum for the major third and major sixth as shown by the full line in Figure 1. To both these intervals corresponds the value $x = 1{\cdot}80$. Taking accordingly $B = 1/3{\cdot}6 = 0{\cdot}2778$, we find in general a distribution of pleasantness values which show the desired maxima. The constant A in equation (5) is scale constant, while C merely determines the zero line. Neither A nor C affect the rank orders, which are determined solely by B. With the above mentioned value of B we find a general correspondence between theory and experiment except for the minor and major seconds and the minor and major sevenths, for which equation (5) gives too high values. In the middle of the musical scale the theory gives too low a value for the tritone. The reason for the discrepancy in the case of the tritone may be as follows. According to the simple scheme here outlined, a mistuning of the interval, *no matter how small,* results in a tremendous increase of both p and q and therefore of x bringing the latter close to 2 and hence decreasing E. Actually a certain finite threshold Δ of mistuning must be reached before we notice it, although Δ is very small. Neurobiophysically we would expect this, considering that two centers, which are too close to each other, may actually overlap and instead of mutually inhibiting they will mutually even enhance each other. For the tritone the value of p/q is very near to $7/5$, the difference between $45/32$ and $7/5$ being only $0{\cdot}0062$. The difference in the ratios p/q for two tones that are one half tone away is about $0{\cdot}1$ (v. Hornbostel, 1927). In other words the distance

(32/45) − (7/5) is much smaller than a tenth of a semitone and would be very likely to be below the threshold Δ. Taking for the tritone $p/q = 7/5$, $x = 1{\cdot}8571$, we bring the theoretical value to a closer agreement with observation. A natural reason for the discrepancy at the ends of the scale may be seen in the possible variation of the mutual inhibition of different centers with the distance between these centers (Rashevsky, 1938, 1940; Landahl, 1938; Householder, 1938). The geometric distance between the centers corresponding to two harmonics will not necessarily be proportional to the distance on the scale of frequencies, but is likely to increase with the latter. But the frequency distance between the non-overlapping harmonics of two tones is the smaller the closer p/q is to either 1 or 2. If the inhibitory effect, which is measured by the constant b of equation (3) first rapidly decreases with distance then to remain appreciably constant above a certain distance, this will have the same effect as increasing the constant B in equation (5) for frequency ratios p/q which are either close to 1 or to 2. A very small increase in B gives an appreciable decrease of E. Making such a correction and putting for the interval No. 1 and No. 11, $B = 0{\cdot}2817$ and for No. 2 and No. 10, $B = 0{\cdot}2799$ we find a rank order curve as shown by the broken line of Figure 1. The full line shows the experimental values obtained by C. W. Valentine (1913), on 146 persons of both sexes. The rank order curves for males and females are slightly different, though show essentially the same trend. We find, however, that the calculated values for the unison and the octave are ridiculously low, way below the seconds and sevenths. This may be due to several causes. First of all we made for simplicity the assumption of equal excitation of all centers. This is very unlikely to happen actually. A center excited by two overlapping harmonics will be excited much more strongly than a center excited by a single harmonic. Since the unison and the octave have the most of overlapping harmonics, our assumption will result in too low calculated values.

Furthermore, if we consider the inhibition as decreasing with distance, it is to be expected that whereas for intervals which are close to the unison and octave, b is going to be larger than for the intervals further removed, yet for the exact unison and exact octave, b will be even slightly smaller than for any other interval. This is to to be expected, because the distance between individual harmonics in a unison or in an octave, measured on the frequency scale, is larger than for any other interval.

Further improvements of the theory should be made by considering the different intensities of excitation for the centers corresponding to different harmonics. If the law of variation of inhibition with

distance is prescribed, the whole problem may be solved graphically, formally in the same way as H. Helmholtz (1870, p. 303) constructed the effects of beats. Analytically the problem may be handled approximately by making b an increasing function of the absolute value of the difference $y = |(p/q) - (3/2)|$, or a function of the linear expression $\alpha|1 - (p/q)| + \beta|2 - (p/q)|$, where α and β are constants, or some other function of p/q.

Possible improvements in those directions shall be considered in subsequent papers.

The interest of the above results lies not so much in the any agreement of theory and observation which both are still too crude as in the circumstance that it shows the applicability to this problem of the general neurological scheme, frequently used in mathematical biophysics.

It must be remembered that the rank order of consonance is not the same as the rank order of pleasantness. Very tentatively we may suggest, that the consonance be measured by the relative amount of inhibition *at a single center*, namely by $1 - bn' = 1 - bnx$. It decreases with increasing x. An alternate possibility however shall be treated in separate papers.

LITERATURE

Beatty, R. T. 1932. *Hearing in Men and Animals.* London: G. Bell and Sons, Ltd.

Helmholtz, H. 1870. *Die Lehre von den Tonempfindungen.* Third ed. Braunschweig: Friedrich Vieweg and Sohn.

Hornbostel, E. M. v. 1927. "Musikalische Tonsysteme" in *Handbuch der Physik,* 8, pp. 446-447. Berlin: Julius Springer.

Householder, A. S. 1938. "Excitation in a Chain of Neurons." *Psychometrika,* 8, 69-73.

Landahl, H. D. 1938. "The Relation Between the Intensity of Excitation and the Number of Neurons Traversed," *Psychometrika,* 3, 291-295.

Rashevsky, N. 1938. *Mathematical Biophysics.* Chicago: The University of Chicago Press.

Rashevsky, N. 1940. *Advances and Applications of Mathematical Biology.* Chicago: The University of Chicago Press.

Valentine, C. W. 1913. "The Aesthetic Appreciation of Musical Intervals in School Children and Adults." *British Jour. of Psych.,* 6, 190-216.

Waetzman, E. 1912. *Die Resonanztheorie des Hörens.* Braunschweig: Friedrich Vieweg and Sohn.

Waetzman, E. 1926. "Hörtheorien." *Handbuch d. norm. u. path. Physiologie,* 11, 667-770. Berlin: T. Springer.

BULLETIN OF
MATHEMATICAL BIOPHYSICS
VOLUME 4, 1942

NON-LINEAR EXCITATION THEORY: NON-ACCOMMODATIVE, SUB-THRESHOLD EFFECTS

ALVIN M. WEINBERG
THE UNIVERSITY OF CHICAGO

The standard two factor excitation theories should be called "pre-excitation" theories since they apply only to those events occurring just up to excitation. A true phenomenological excitation theory which describes the *whole* excitation cycle must involve non-linear equations. The nature of these non-linearities is suggested by B. Katz's subthreshold response data. From this data is constructed a "local phenomenological characteristic" which is analogous to the current-voltage characteristic of a non-linear electrical or mechanical system capable of displaying relaxation oscillations. Excitation by constant currents is shown to occur where the slope of the characteristic changes sign. The variation of the time constant of excitation with degree of response, explained by W. A. H. Rushton in terms of a liminal length, is described here in purely formal terms. The theory as presented explicitly treats only those events in the excitation cycle up to and a little beyond excitation; the complete excitation cycle (including recovery and repetition) is mentioned as being amenable to mathematical treatment by an extension of the present theory.

The formal two-factor theory of nerve excitation, (e.g., Rashevsky, 1933) while being adequate to predict time-intensity relations for a variety of stimulating currents, is generally assumed to be inadequate to deal with phenomena occurring after "physiological" response has begun. (See, however, Katz, 1936). That this inadequacy must be fundamental is apparent from a consideration of the physical basis underlying excitation: profound structural changes are known to accompany excitation and recovery (Cole and Curtis, 1938), yet the excitation equations involve parameters which are constant and, therefore, independent of these changes. A possible way out of this dilemma has been suggested by several authors (Monnier and Coppée, 1939; Arvanitaki, 1939; Householder, 1939): viz., that the excitation equations are really *non-linear*, and that the usual linear equations, which are valid only during the "physical" response, are first approximations to the exact equations. (This statement may be taken to imply a definition of physical response: i.e., physical response is that response representable by linear equations.) Such a non-linear theory could presumably describe the processes accompanying breakdown and

recovery; however, so far as the writer is aware,[1] no attempt has been made to investigate the specific nature of the required non-linearities. In the present paper we shall investigate some possible non-linear modifications of the formal excitation theory; the discussion will be confined to non-accommodative (single-factor) cases, and for the most part, to sub-threshold effects.

Phenomenological character of excitation theory. The "state of excitation" of a nerve, ε, is defined operationally by

$$\varepsilon(t) = \frac{E_0 - E(t)}{E_0}, \tag{1}$$

where E_0 is the resting threshold cathodal impulse (measured either in volts or coulombs), and $E(t)$ is the impulse required to just bring the nerve to threshold at time t. Before excitation $E(t)$ is the shock required to just produce a propagated excitation, and so $E(t)$ is cathodal and $\varepsilon(t) < 1$; during the early stages of excitation $E(t)$ is the shock required to just quench the excitation, $E(t)$ is anodal, and $\varepsilon > 1$. Thus, although the intrinsic physical nature of ε is a matter of conjecture, ε can be defined operationally over a considerable portion of the excitation cycle; over this portion of the cycle it is a perfectly valid variable to use as the basis of a mathematical theory of excitation (Monnier, 1934; Schaefer, 1940, p. 166).

It has been shown (Young, 1941) that if ε is assumed to vary according to

$$\frac{d\varepsilon}{dt} = KI - k\varepsilon, \tag{2}$$

then ε defined by (1) is consistent with (2). Proof of this is required because any dynamic equation such as (2) implies a relation between ε and the current I [or $E(t)$] which, in general, will not reduce to (1) for impulsive stimuli. If (2) is modified by assuming that k is itself a function of ε, but K is not, then we have

$$\frac{d\varepsilon}{dt} = KI - k(\varepsilon)\varepsilon \cdot \tag{3}$$

it remains to show that ε defined by (3) is consistent with (1).

Let us define two quantities ε' and ε'' which vary according to

$$\frac{d\varepsilon'}{dt} = KI - k'\varepsilon'$$

[1] During the preparation of this manuscript I have had the opportunity to read a very interesting manuscript by Dr. B. Katz in which a semi-physical approach to the problems discussed here is given.

and

$$\frac{d\varepsilon''}{dt} = KI - k''\varepsilon''$$

where k' and k'' are the maximum and minimum values, respectively, of $k(\varepsilon)$ on the range 0 to ε. Then it is clear that

$$\varepsilon' \leqq \varepsilon \leqq \varepsilon'',$$

the equality holding, for any arbitrary $I(t)$, only for constant $k(\varepsilon)$. Moreover, for impulsive shocks (Young, 1941),

$$\varepsilon' = \varepsilon'' = \frac{E_0 - E(t)}{E_0}$$

and so $\varepsilon(t)$ of equation (3) is also given by (1). We have therefore proved that *the dependent variable of the non-linear excitation equation* (3) *is operationally definable by* (1). We shall refer to a theory which concerns itself only with variables definable in terms of the state of excitation as a *phenomenological* theory; from this point of view, the single-factor theory or its non-linear generalization (3) is phenomenological.

The fact that k is a function of the electrode spacing (Katz, 1939, p. 75) would decrease the operational significance of ε, unless we agree upon some standard electrode spacing; in the remaining discussion we shall assume that this standard electrode spacing is maintained.

Subthreshold effects. Experiments by B. Katz (1937), A. L. Hodgkin (1938), R. J. Pumphrey et al (1940), and others on subliminal responses of nerve have strongly indicated that the linear equation (1) should be replaced by the more general equation (3). Their evidence may be briefly summarized as follows: after an impulsive conditioning shock, ε will attain some value, ε_1, and according to (2), will then subside exponentially, i.e.,

$$\frac{d\varepsilon}{dt} = -k\varepsilon; \quad \varepsilon = \varepsilon_1 e^{-kt}, \tag{4}$$

where k is the time constant of excitation. (Note that our k is the reciprocal of Hill's k). This statement is the starting point of A. V. Hill's (1936) discussion of excitation. The exponential subsidence of the excitatory state is certainly correct if ε_1 is small or negative (anodal); but, as Katz's (1937) Figure 4 shows, when $\varepsilon_1 > .5$ marked deviations from (4) occur, while for $\varepsilon_1 > 1$, ε actually increases with time. An interpretation of these deviations from linearity in terms of a "local" response in accordance with Rushton's notion of liminal

length (1937) has been fairly general (Katz, 1939); but from the strictly *phenomenological* viewpoint such considerations are somewhat irrelevant. All that can be concluded from these curves is that the differential equation (4) should be replaced by a non-linear equation in which the time constant is itself a function of ε, (or, a possibility which will not be discussed here, K is a function of I). The physical interpretation of such a non-linearity is outside the scope of a *formal* theory. For example, from the point of view of a formal non-linear theory, it is immaterial whether a variable k is due to an all-or-none local response extended over a gradually increasingly area, or a graded local response, or (as would appear to be most likely a priori) a combination of both.

From the $\varepsilon(t)$ curves of Katz's experiment, the function $k(\varepsilon)$ (which we shall call the instantaneous time constant) can be found since, by (4),

$$k(\varepsilon) = -\frac{1}{\varepsilon}\frac{d\varepsilon}{dt}, \tag{5}$$

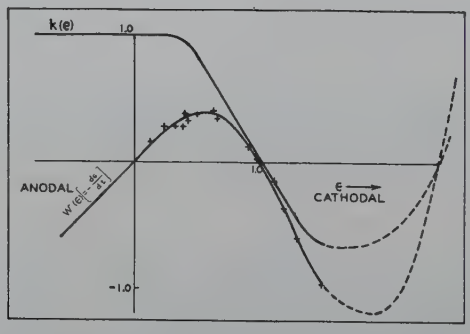

FIGURE 1

The "local phenomenological characteristic", $w(\varepsilon)$ vs. ε, and the instantaneous time constant $k(\varepsilon)$, from Katz's data. Indicated points are experimental. The dotted portions of these curves are hypothetical. The function $k(\varepsilon)$ for anodal shocks is a constant whose value is uncertain (cf. Katz, 1937); for this reason no experimental points are shown on the anodal side.

and the value of $d\varepsilon/dt$ for each value of ε can be ascertained by graphical differentiation. If k is a function of ε alone, these $\varepsilon(t)$ curves should consist of a family of "parallel" curves, in which the slope of each member of the family is the same for a given value of ε. To what extent this is true can be judged from Figure 1, where $-d\varepsilon/dt$ vs. ε and $k(\varepsilon)$ are plotted from Katz's data; very much the same results are found from the giant axon data of R. J. Pumphrey *et al.* The scattering of the points taken from different members of the decay curve suggests that k may depend on some variable besides ε (e.g., $d\varepsilon/dt$, ε_1,

or I) or that even in this range K is not constant; however, the scattering is not bad between $\varepsilon \sim .5$ and $\varepsilon \sim 1.4$ and so we shall suppose k to be determined by ε alone in the present discussion.

A semi-analytic approximation to $k(\varepsilon)$ together with the response curves obtained by using this approximation in integrating (5) are shown in Figure 2. A general resemblance to the experimental

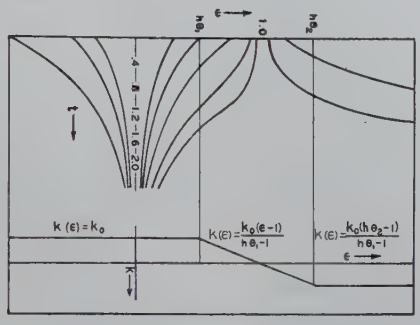

FIGURE 2

Local decay curves obtained by integrating (5) with $k(\varepsilon)$ given by the piecewise linear function on the right. (The positive direction on the k-axis is right to left.) The notation $h\ \theta_1$ and $h\ \theta_2$ for the points at which $k(\varepsilon)$ changes slope is suggested by Rushton (1937), Figure 6.

curves is apparent here; improving the fit by bettering the approximation to $k(\varepsilon)$ is of no particular theoretical value, however.

The nerve "phenomenological characteristic". In the non-linear theory of electrical oscillations and related phenomena it is customary to introduce a "characteristic curve", a knowledge of which is sufficient to predict the behavior of the system provided the dynamical equations of the system are known. In general, the characteristic gives the relation between a current and a potential variable; if the current variable is a multiple valued function of the potential variable, the characteristic is usually denoted by the letter N (north), while if the potential variable is a multiple valued function of the current, the characteristic is denoted by S (south) (cf. le Corbellier, 1931, p. 32). For systems possessing a linear characteristic, the variational resistance (defined as the slope of the characteristic) is constant and equal to the ordinary resistance. While the system is in a state characterized by positive resistance, energy must be supplied from the outside to maintain the activity of the system; while the system is in a state characterized by negative resistance, the system supplies its own energy. From the definition of the characteristic, it follows that the variational resistance (or conductance) changes sign at a turning point of the characteristic.

In attempting to arrive at a corresponding "characteristic" for nerve based on phenomenological principles (assuming that one exists), we are guided by certain requirements, suggested by the electrical analogies, which must be satisfied by any curve which plays the role of a characteristic in the theory. First, the characteristic must be a relation between some variable which behaves like a potential (cf. Herrenden-Harker, 1940), and a variable which has the dimensions of current (in a generalized sense). Second, the slope of the characteristic must reduce, in the linear case, to a variational conductance (or a time constant, in circuits with constant capacitance). This means that a theory based on a linear characteristic must be identical with the linear theory already known. Third, at the turning points of the characteristic, the direction of the energy flow must reverse, and the nerve phenomenon must become self-sustaining.

We can treat the quantity ε as a potential variable without compromising our ideas of potential too seriously. For the equilibrium state of the nerve is characterized by the condition $\varepsilon = 0$, and the value of ε is a measure of the deviation from equilibrium. Consequently, the potential energy of the system (in a strict physical sense) can be expanded in powers of ε, thus establishing a connection between ε and the potential energy which is valid even though ε is a purely phenomenological variable. The quantity ε is analogous to the displacement variable in a spring near equilibrium.

On the other hand, the choice of current variable is not so clear. The quantity $w(\varepsilon) = k(\varepsilon)\varepsilon \left[= \frac{-d\varepsilon}{dt} \text{ by (5)} \right]$ satisfies the dimensional requirement, and when k is constant, it does give rise to a linear "characteristic" which yields the original linear theory. However, if we plot $w(\varepsilon)$ vs. ε (Figure 1), we find that the turning point of this "local phenomenological characteristic" (l.p.c.) occurs almost where the physiological local response begins, but certainly *not* where the excitation has become self-sustaining. The origin of this difficulty seems to lie in the fact that the self-sustaining nerve response is a propagated disturbance; *the criteria for physiological response and for propagated response are not identical.* This fact was pointed out by W. A. H. Rushton in 1937.

Stability and instability of the characteristic. If we assume that K is independent of ε, (an assumption which is certainly incorrect for $\varepsilon >> 1$, and may be incorrect even for smaller ε), we can indicate the effect of a constant current I by means of a straight line drawn across the l.p.c. parallel to the ε axis, (Figure 3); the line KI intersects the characteristic at the points A and B. Point A is seen to be stable,

for if the state of the nerve is represented by some point A, and if we displace this point toward the right (ε increasing), $KI - w(\varepsilon)$, or by equation (3), $d\varepsilon/dt$, becomes negative and the point returns to A; similarly if ε is decreased slightly, $KI - w(\varepsilon) > 0$ and again the point returns to A. On the other hand, a displacement in either direction from the point B will tend to increase the displacement ($d\varepsilon/dt$ and $\Delta\,\varepsilon$ have the same sign) and so B is unstable. The argument presented here can easily be generalized to show that for steady current stimulation any point on an ascending branch of the l.p.c. ($dw/d\varepsilon > 0$) is stable while any point on a descending branch ($dw/d\varepsilon < 0$) is unstable.

Suppose a graded series of constant stimuli are applied to a resting nerve; these may be represented by a family of horizontal lines as in Figure 3. From the preceding discussion, it is clear that a con-

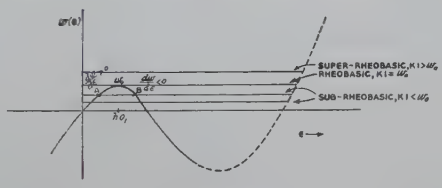

FIGURE 3
Stability and instability of the l.p.c. for steady current stimulation.

stant current, I, will not stimulate if KI intersects the ascending branch of the l.p.c. The rheobase will be represented by the line which is tangent to the l.p.c., or, from the figure,

$$I_0 = \frac{w_0}{K}$$

where w_0 is the maximum value of $w(\varepsilon)$ and I_0 is the rheobase. From a knowledge of the l.p.c. we can predict the response to a constant current stimulus: if $I > w_0/K$, excitation will occur, otherwise not.

The response to impulsive stimuli presents certain difficulties if we wish to make our interpretation depend on the properties of the l.p.c. As we have said, the turning point of the local characteristic is known experimentally to occur at about $\varepsilon = .5$ instead of $\varepsilon = 1$; in other words, instability to steady current stimulation occurs before instability to impulsive stimulation. Just such a possibility was suggested by Rushton (cf. his θ_1 with $h\,\theta_1$) in discussing the "liminal length"; if stimulation is impulsive, the entire liminal length must be excited for instability to set in (i.e., the representative point must be brought to the zero of the l.p.c.) while if stimulation is steady, instability induced at any one point is sufficient to ensure propaga-

tion (i.e., the representative point need merely be brought to the *turning point* of the l.p.c.). This picture is very suggestive—but since it is based on the assumption that the local response is all-or-none, we are not justified in accepting it as the complete explanation of the difference in response to impulsive and steady stimuli.

Thus far we have intentionally neglected any discussion of what happens to the representative point an appreciable time after instability has set in. To answer this question we would have to know the shape of the l.p.c. during the later part of the action. It is difficult to assign operational significance to the quantity ε during the later stages of the action, since, as far as the writer is aware, it is impossible to block propagation by impulsive anodal shocks applied at the point of stimulation after a certain point in the action has been reached. If it eventually proves possible to give an operational definition of ε during the subsidence of the action (Monnier, 1934), we would certainly find it hard to refrain from extending the characteristic to include a second ascending branch (dotted line, Figure 1). Such a characteristic (S type), together with suitable assumptions concerning the variation of K with ε, would enable us to give a phenomenological theory of such processes as recovery and repetitive discharge. The analogy with systems capable of displaying relaxation oscillations would be complete. However, we do not feel justified in going further into these possibilities until some evidence is given for extending the characteristic in the manner just described.

Relations between linear and non-linear theory. It is an empirical fact that the linear equation (2) predicts excellent strength-duration and voltage-capacity curves. If (2) is only an approximation to the non-linear (3), why should this be the case?

Suppose voltage-capacity or strength-duration experiments are performed in which the index of response is not necessarily the propagated disturbance ($= 1$), but some arbitrary value of the excitatory state, ε_h, as measured by the test shock method. Voltage-capacity measurements of almost this type have been performed by H. Rosenberg (1937) but technical difficulties have made the corresponding strength-duration experiments unfeasible (although cf. Rushton, 1932). If ε_h is small ($< .5$) so that the linear theory applies, the time constant found from such experiments would simply be the initial slope of the l.p.c., and would be independent of degree of response. As ε_h increases, the linear theory no longer applies: the effective time constant will depend on ε_h and, in general, on the shape of the stimulating current.

To determine exactly what intermediate value of k must be used in a linear theory strength-duration curve so that it will deviate as

little as possible from the non-linear strength-duration curve, we must require that the duration of a constant stimulus according to the non-linear theory,

$$\int_0^{\varepsilon_h} \frac{d\varepsilon}{KI - k(\varepsilon)\varepsilon}$$

and the duration according to the approximating linear theory

$$\int_0^{\varepsilon_h} \frac{d\varepsilon}{K_l I - k_l(\varepsilon_h)\varepsilon}$$

be as nearly alike as possible, for a given index of response ε_h. The quantities K_l and $k_l(\varepsilon_h)$ are the approximating linear theory constants for the index of response ε_h. An exact solution of this minimum problem for all currents $I(t)$ seems to be very difficult, and so we shall simply write down an approximate solution which is valid for large values of the stimulating current:

$$k_l(\varepsilon_h) = \frac{2}{\varepsilon_h^2} \int_0^{\varepsilon_h} k(\varepsilon)\varepsilon d\varepsilon\,, \qquad K_l = K\,. \tag{6}$$

This integral is the first moment of the function $k(\varepsilon)$. The fact that $k_l(\varepsilon_h)$ is not independent of I in the next approximation (small values of I) may be related to H. A. Blair's (1936) contention that the simple linear theory is inadequate, even for strength-duration data.

To determine voltage-capacity or strength-duration curves accurately we should integrate (3) with the function $I(t)$ replaced by the particular current used as stimulus. The result of this integration for constant currents of various intensities, is given in Figure 4*a*. (The $k(\varepsilon)$ function of Figure 2 was used here.) These curves are practically the same as those given by W. A. H. Rushton (1937, Figure 6).

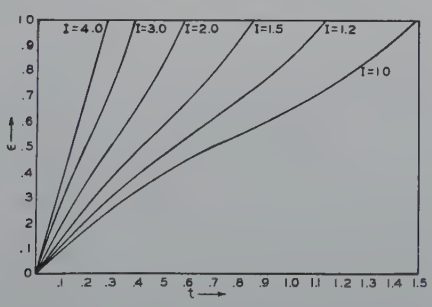

FIGURE 4*a*

The variation of ε under constant current stimulation obtained by integrating (3) with the $k(\varepsilon)$ of Figure 2. The parameters in Figure 2 are arbitrarily taken: $k_0 = 1$, $h\,\theta_1 = .5$, $K = 1$, and the units of t and I are arbitrary.

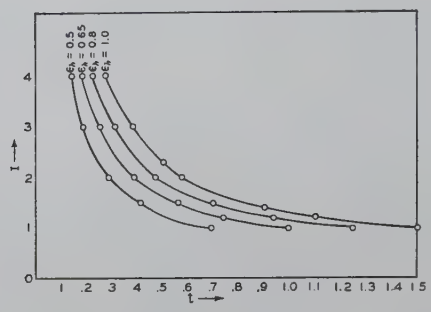

FIGURE 4*b*

Strength-duration curves for indices of response $\varepsilon_h = 1$, .80, .65, .50. Points obtained directly from the curves of Figure 4*a* are represented by circles. The curves were obtained by using the Table 1 values of $k_l(\varepsilon_h)$ in the ordinary condenser formula (2).

From the curves of Figure 4*a*, we can construct strength-duration curves for any arbitrary index of response; the curves for $\varepsilon_h = 1$, .8, .65, .5 are given in Figure 4*b*. The values of $k_l(\varepsilon_h)$ determined directly from these curves, together with theoretical values of $k_l(\varepsilon_h)$ calculated from (6), are given in the accompanying Table 1. The magnitude of the variation in $k_l(\varepsilon_h)$ which may be expected is seen to be of the order of 100%; this agrees with the results of H. Rosenberg (1937) and of B. Katz (1937).

Table 1: Values of $k_l(\varepsilon_h)$ from strength-duration curves (Figure 4*b*) compared with values of $k_l(\varepsilon_h)$ from (6).

ε_h	$k_l(\varepsilon_h)$ (Fig. 4*b*)	$k_l(\varepsilon_h)$ (Eq. 6)	% difference
.5	1.0	1.0	0
.65	.86	.92	6+
.80	.74	.79	6+
1.0	.54	.58	7+

It is seen from Figure 4*b* that the non-linear strength-duration curves are practically identical with the linear curves which are obtained by integrating the linear equation (2), after replacing k_0 by $k_l(\varepsilon_h)$. This must be considered rather fortuitous, since, by taking some different approximating function for $k(\varepsilon)$, we could get a different non-linear strength-duration curve. Thus it appears that Rushton's prediction of a strict linear theory strength-duration curve, even when the liminal length is taken into account, must depend on the assumption of an all-or-nothing response at a point.

Physical interpretations. Although the theory which we have outlined is phenomenological, certain connections with physical interpre-

tations seem to be inevitable. As an example, we may ignore the difficulties for the moment, and identify ε with the condenser voltage, V, in a circuit consisting of a condenser, C, shunted by a non-linear resistance. For this circuit, assuming no current flow from the outside,

$$\frac{dV}{dt} = -\frac{V}{R(i)C}$$

where i is the current through the variable resistance $R(i)$ and, by definition, $iR(i) = V(i)$. Since $i = C\frac{dV}{dt}$, the $V(i)$ characteristic may be determined exactly as we determined $w(\varepsilon)$—by graphically differentiating a family of voltage decay curves. The $V(i)$ curve may be identified with our $w(\varepsilon)$ provided we plot ε vertically and w horizontally; on the other hand, this characteristic bears little resemblance to the steady state $V(i)$ curve found by K. S. Cole and H. J. Curtis (1940) for squid axon.

The direct measurement of the $V(i)$ characteristic in nerve is analogous to the usual direct measurement (with ammeter and voltmeter) of the characteristic of a neon tube shunted by a resistance and a condenser. However, there is another "phenomenological" method of measuring the characteristic of such a neon tube which, while highly impractical, is analogous to the scheme we have used here to get at the "characteristic" of nerve (cf. also Blinks and Skow, 1940). Suppose, instead of directly measuring the current as a function of the steady voltage across the tube, we determine the time course of the discharge of the condenser through the neon tube and its shunting resistance. This may be done either by actually measuring the time decay of the initial charge with a ballistic galvanometer, or, by determining the extra charge required at each time to just cause the neon tube to flash. In this way we can obtain "local excitatory decay" curves entirely analogous to those found by Katz, and from these we can determine the instantaneous voltage across the tube as a function of the current through it. For a simple neon tube circuit this phenomenological method and the previous direct method should give identical characteristics. If the experiments of K. S. Cole and H. J. Curtis may be considered the proper analogue, in the nerve, to the direct measure of the characteristic of the neon tube, then as we have mentioned, the direct and the phenomenological methods in nerve *do not* lead to the same characteristics. The explanation of this difference probably lies in the inadequacy of the structural assumptions required to make the transition from the phenomenological to the physical characteristics. A complete elucidation of this difference will be a major task of any adequate theory of nerve activity.

This work was aided in part by a grant from the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.

LITERATURE

Arvanitaki, A. 1939. "Recherches sur le Réponse Oscillatoire Locale de l'Axone Géant Isole de Sepia." *Arch. Int. Physiol.*, **49**, 209-256.

Blair, H. A. 1936. "The Kinetics of the Excitatory Process." *Cold Spring Harbor Symp.*, **4**, 63-72.

Blinks, L. R., and R. K. Skow. 1940. "The Electrical Capacity of Valonia." *Jour. Gen. Physiol.*, **24**, 247-261.

Cole, K. S., and H. J. Curtis. 1938. "Electric Impedance of Nitella During Activity." *Jour. Gen. Physiol.*, **22**, 37-64.

Cole, K. S., and H. J. Curtis. 1941. "Membrane Potential of the Squid Giant Axon During Current Flow." *Jour. Gen. Physiol.*, **24**, 551-563.

Cole, K. S. 1941. "Rectification and Inductance in the Squid Giant Axon." *Jour. Gen. Physiol.*, **25**, 29-51.

le Corbellier, Ph. 1931. *Les Systèmes Autoentretenus et les Oscillations de Relaxation.* Paris: Hermann.

Herrenden-Harker, G. F. 1940. "Relaxation Oscillations." *Am. Jour. Physics.*, **8**, 1-22.

Hodgkin, A. L. 1938. "Subthreshold Potentials in a Crustacean Nerve Fiber." *Proc. Roy. Soc. B.*, **126**, 87-121.

Householder, A. S. 1939. "Studies in the Mathematical Theory of Excitation." *Bull. Math. Biophysics*, **1**, 129-141.

Hill, A. V. 1936. "Excitation and Accommodation in Nerve." *Proc. Roy. Soc. B.*, **119**, 305-355.

Katz, B. 1936. "Multiple Response to Constant Current in Frog's Medullated Nerve." *Jour. Physiol.*, **88**, 239-255.

Katz, B. 1937. "Experimental Evidence for a Non-Conducted Response of Nerve to Subthreshold Stimulation." *Proc. Roy. Soc. B.*, **124**, 244-276.

Katz, B. 1939. *Electric Excitation in Nerve.* London: Oxford University Press.

Monnier, A. 1934. *L'excitation Électrique des Tissus.* Paris: Hermann.

Monnier, A., and G. Coppée. 1939. "Nouvelles Recherches sur la Resonance des Tissus Excitables I. Relation entre la Rhythmicité de la Réponse Nerveuse et la Résonance." *Arch. Int. Physiol.*, **48**, 129-179.

Pumphrey, R. J., O. H. Schmitt, and J. Z. Young. 1940. "Correlation of Local Excitability with Local Physiological Response in the Giant Axon of the Squid (Loligo)." *Jour. Physiol.*, **98**, 47-72.

Rosenberg, H. 1937. "Electrotonus and Excitation in Nerve." *Proc. Roy. Soc. B.*, **124**, 308-336.

Rashevsky, N. 1933. "Outline of a Physico-Mathematical Theory of Excitation and Inhibition." *Protoplasma*, **20**, 42-56.

Rushton, W. A. H. 1932. "A New Observation in the Excitation of Nerve and Muscle." *Jour. Physiol.*, **75**, 16-17.

Rushton, W. A. H. 1937. "Initiation of the Propagated Disturbance." *Proc. Roy. Soc. B.*, **124**, 210-243.

Schaefer, H. 1940. *Elektrophysiologie.* Vienna: F. Deuticke.

Young, G. 1941. "On Reinforcement and Interference Between Stimuli." *Bull. Math. Biophysics*, **3**, 5-12.

SCOPE OF THE BULLETIN

1. The Bulletin is devoted to publications of research in Mathematical Biophysics, as contributing to the physicomathematical foundations of biology in their most general scope.

2. Papers published in the Bulletin cover physicomathematical theories as well as any other mathematical treatments of biological phenomena, with the exception of purely statistical studies.

3. Mathematical studies in physics or in borderline fields in which a direct connection with biological problems is pointed out are also accepted.

4. Emphasis is put upon the mathematical developments, but a description and discussion of experimental work falls also within the scope of the Bulletin provided that description or discussion is made in close connection with mathematical developments *contained in the same paper*.

5. Outside of the scope of the journal are papers of purely statistical nature or papers concerned only with empirical equations.

PREPARATION OF MANUSCRIPTS

All manuscripts should be typewritten double space. Equations should be numbered on the right consecutively. *Do not* use such notations as "equation 2a" or, "equation 5′" etc. References should be all given at the end of the paper, arranged in alphabetic order by authors and for each author chronologically, following *exactly* the style used in the Bulletin. In text, reference should be made by giving in parentheses the name of the author followed by the year of publication. In case of several publications by the same author in the same year, use notations "1940a", "1940b", etc.

In writing equations, slanted lines should be used wherever possible.

Every paper is to be preceded by a short abstract.

Drawings should be prepared in a professional manner on white paper or tracing cloth following as closely as possible the style used in the Bulletin. They should be drawn approximately twice the scale of the finished reproduction. Lettering should be made by means of a lettering guide. If desired by the authors, drawings may be made at the Editorial Office according to author's instructions, at cost.